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real-world evidence on treatment and outcomes

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General Introduction and Outline of Thesis

Numbers

Renal cell carcinoma (RCC) accounts for approximately 2-3% of all cancers diagnosed worldwide, making it the 14th most common malignancy[1-3]. In 2022, there were approximately 434,840 patients diagnosed with RCC and 55,953 deaths[1]. The incidence of RCC has been steadily increasing over recent decades, particularly in Western countries where the highest rates are observed[2]. In the Netherlands, the absolute number of newly diagnosed RCC cases increased from approximately 1,500 in 2000 to on average 2,800 in recent years, with a further rise expected to 3,600 cases by 2032[4]. Approximately 20% of patients present with metastases at the time of diagnosis (synchronous metastatic RCC), and an additional 20–40% of patients with localised disease develop metastases during follow-up (metachronous metastatic RCC)[5].

RCC occurs more frequently in men, who comprise about 65% of cases, and predominantly affects older individuals[6]. The majority of patients are diagnosed between the ages of 60 and 75, with a median age at diagnosis of 68 years in the Netherlands[7]. The most common histological subtype is clear cell RCC (70%), followed by papillary RCC (10-15%) and chromophobe RCC (5%)[6].

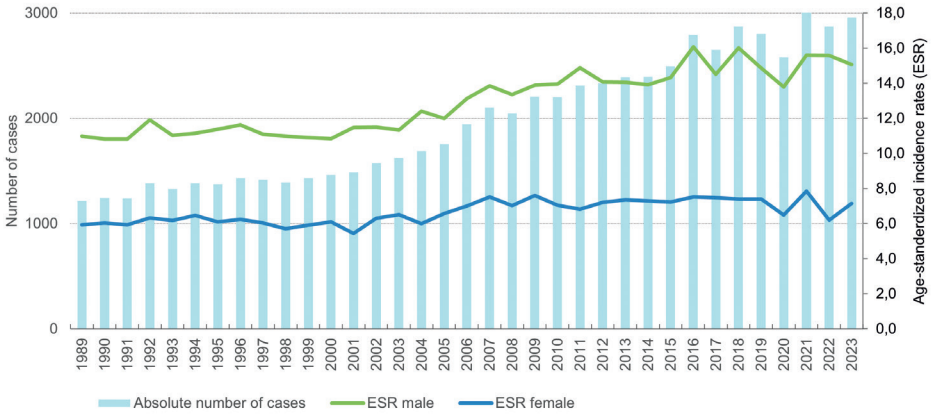

Figure 1. Incidence of renal cancer (absolute numbers and age-standardised rate per 100,000 person-years) between 1989-2023 (ESR: European Standardised Rate).

Adapted from: IKNL. Cijfers over Nierkanker.[7]

Risk factors

Established risk factors for developing RCC are smoking, obesity and hypertension[2,6]. Current smokers have a higher risk of developing RCC compared to non-smokers. This risk is directly associated with smoking intensity and duration. The risk of developing RCC decreases over time after cessation. The risk for current smokers is 39% versus 26% for ever smokers versus 20% for never smokers[8]. A history of hypertension is associated with 67% increased risk of RCC, and each 10-mmHg increase in blood pressure is associated with 10-22% increased risk of RCC[9]. Obesity is also strongly related to RCC with a 4% increase in RCC risk for every point increment in body mass index (BMI)[10]. Additionally, chronic kidney disease contributes to RCC development, particularly end-stage renal disease or kidney disease requiring long-term dialysis[11]. In contrast, regular physical activity appears to have a protective effect, reducing RCC risk, potentially through its role in lowering body weight and improving blood pressure regulation[12].

The rising prevalence of obesity, smoking, and hypertension in the recent decades is thought to have contributed to the global increase in RCC incidence, especially in high-income countries and is expected to continue to contribute to this trend in the coming years[4,13].

In addition to life-style related risk factors, genetic and hereditary factors also play a role in RCC development. Approximately 5-8% of RCC cases are hereditary and occur as part of familial cancer syndromes, such as von Hippel-Lindau (VHL) disease, hereditary leiomyomatosis and renal cell carcinoma (HLRCC), and Birt-Hogg–Dubé syndrome. These syndromes are typically associated with an earlier onset of disease, often with bilateral or multifocal tumors[6,14].

Diagnosis and staging

The classical triad of haematuria, flank pain, and flank mass is rarely seen, as the majority of RCC cases are incidentally detected (approximately 60%) on abdominal imaging performed for other reasons before the development of symptoms[6,15]. The increased use of abdominal imaging and subsequent incidental detection has most likely attributed as well (in addition to life style related factors) to the rise in RCC incidence, especially in earlier stages[16,17].

Diagnostic work-up includes imaging with computed-tomography (CT)-scan with intravenous contrast administration. Magnetic Resonance Imaging (MRI)-scan or Contrast Enhanced Ultrasound (CEUS) can be used as additional work-up or sometimes as alternative to the conventional CT-scan[14]. Percutaneous biopsy for histological assessment is important in selected patients. It is particularly valuable for appropriately identifying patients for active surveillance, obtaining a definitive histological diagnosis prior to ablative treatments, and guiding the selection of the most suitable treatment strategy in metastatic RCC.

The Tumour Node Metastasis (TNM)-Classification is the most clinically and scientifically used classification for RCC. Tumour size, tumour invasion, lymph node involvement and distant metastasis are included in the International Classification for Oncology (ICD-O)[18,19]. Tumours limited to the kidney and measuring up to 7 cm are categorised as Stage I. This includes T1a tumours (<4 cm), also referred to as small renal masses (SRMs), and T1b tumours (4–7 cm). Tumours larger than 7 cm that are still limited to the kidney are classified as Stage II (T2). Stage III RCC is characterised by local invasion into major veins (renal vein or vena cava) or perinephric tissues, regardless of tumour size (T3). Stage IV, or locally advanced/metastatic disease, includes tumours that extend beyond the Gerota's fascia or into the ipsilateral adrenal gland (T4), involve regional lymph nodes (N1), or present with distant metastases (M1).

Prognosis in patients with metastatic RCC is further stratified using the International Metastatic RCC Database Consortium (IMDC) criteria. This model assigns one point for each of the following six adverse prognostic factors: Karnofsky performance status <80%, time from diagnosis to initiation of systemic therapy <1 year, decreased haemoglobin level, hypercalcemia, neutrophilia, and elevated platelet count. Based on the total number of risk factors, patients are stratified into three groups: favourable risk (0 factors), intermediate risk (1–2 factors), and poor risk (≥3 factors). This classification is widely used to predict survival and to guide therapeutic decision-making in clinical practice.

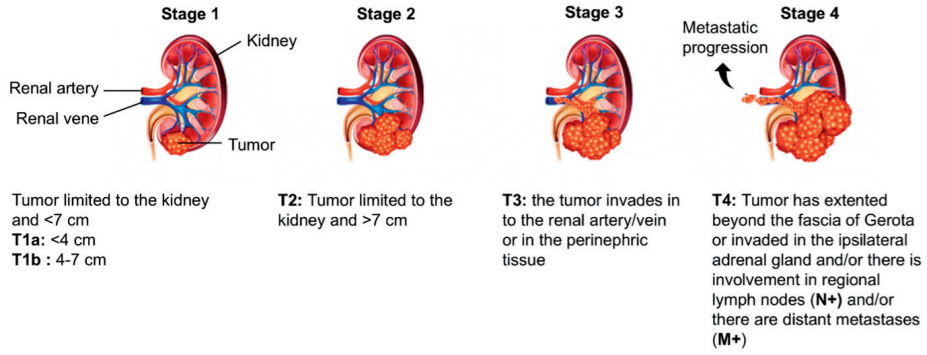

Figure 2. RCC stages based on TNM classification (7th edition).

Licensed from Adobe Stock. Diagram showing different stages of kidney cancer [illustration]. April 2025 (ID: 195276613)

Clinical management

The standard of care for RCC varies and is largely determined by the stage of the disease. Treatment decisions should be made through a shared decision-making process, carefully considering patient-specific factors such as comorbidities, life expectancy, and personal preferences.

Localised RCC

Over the past several decades, there has been a significant shift in the management of T1 RCC from radical nephrectomy (RN) to partial nephrectomy (PN), which has become the standard of care due to its nephron-sparing benefits. PN reduces the risk of developing cardiovascular disease and mortality[20-22]. If partial nephrectomy is technically not feasible, RN may still be an alternative although the risks and benefits of PN versus RN should be weighed on individual patient- and tumour characteristics. Preoperative risk assessment tools such as the RENAL and PADUA nephrometry scores can aid in evaluating tumour complexity and guiding surgical planning[23]. Alternative ablative nephron-sparing treatment options are available if needed. For larger localised tumours, radical nephrectomy (RN) remains the recommended treatment.

Alternative nephron-sparing management are increasingly accepted as a less-invasive strategy for T1a RCC[24]. Active surveillance (AS) has been shown to be safe in selected patients with SRMs, particularly in older patients and those with

comorbidities[25,26]. In addition, focal therapy (FT) is established as a minimally invasive option for cT1a RCC due to a lower risk of complications compared to PN[27,28]. In recent years, stereotactic radiotherapy has gained acceptance as a novel minimally-invasive approach for RCC, possible also for larger tumours. However, its definitive role has not yet been defined[29].

Over time, surgical techniques for RCC have evolved from open procedures to minimal invasive approaches, including laparoscopic and, more recently, robot-assisted surgery. Laparoscopic surgery for RCC is associated with reduced morbidity, shorter hospital stays and decreased need for analgesia compared to open surgery[21,30,31]. While robot-assisted RN has not shown superiority over laparoscopic RN[32], robot-assisted PN is associated with several advantages, such as lower conversion rates to open surgery, shorter warm ischaemia time, less blood loss, smaller change in post-operative GFR and shorter hospital stay compared to a laparoscopic approach[33,34].

Metastatic RCC

The treatment landscape of mRCC has undergone significant changes in recent decades. In the cytokine era, interferons were the only available treatment for metastatic RCC, until 2006, when the introduction of targeted therapies, specifically tyrosine kinase inhibitors (TKIs) marked a significant advancement. More recently, the emergence of immunotherapy (IO) has marked a new era of treatment. Since 2019, the combination of ipilimumab and nivolumab is approved as first-line therapy in the Netherlands for patients with intermediate and poor IMDC risk[5]. Today most patients with metastatic RCC are treated with IO combination therapy (IO + IO) in the first-line setting, or with IO combined with a TKI agent (IO + TKI), while TKI monotherapy is reserved for patients who are unable to tolerate IO combinations, those with specific non–clear-cell RCC subtypes, or patients with favourable risk clear-cell mRCC[14].

In the metastatic setting, treatment is largely guided by metastatic volume and burden. Patients with low tumour burden and slow-growing metastases are considered for active surveillance and do not receive direct systemic therapy[35]. Unfortunately, not all patients are considered suitable for systemic therapy, and best supportive care is not uncommon[5].

In patients with oligometastatic disease (metastases limited in number and location, usually 1-5 metastatic lesions)[36], cytoreductive nephrectomy (CN) (with or without metastasectomy or lymph node dissection) could be performed.

Upfront CN was considered the standard of care in the cytokine era, but this benefit was questioned in the targeted therapy era by the two pivotal trials CARMENA and SURTIME[37,38]. Based on these results, upfront CN is no longer standard of care. Instead, patients responding to systemic therapy might be considered for deferred CN[39]. However, in the current immunotherapy era, it is hypothesised that upfront CN may enhance IO efficacy by reducing tumour-derived immunosuppressive factors. Currently, the exact role of CN remains unclear: timing and selection of patients have yet to be determined[39,40].

Volume standards and centralisation of RCC care

PN is a complex procedure and has been associated with higher complication rates compared with RN[41-43]. Higher hospital volumes have been associated with decreased risk of conversion, positive surgical margins and complication rates[44,45]. Furthermore, previous research showed that treatment in a high-volume hospital is associated with a higher probability of PN compared with RN for cT1a tumours. In 2018, the Dutch Association of Urology (Nederlandse Vereniging voor Urologie, NVU) introduced minimal surgical volume standards for hospitals performing PN and/or RN. Since then, hospitals are required to perform a minimum of 10 RNs annually, while for PNs, a minimum of 10 procedures per year is mandated (three-year average). In 2024, these minimum volume standards were revised and, since then, hospitals should perform at least 20 oncological kidney surgeries annually. The same applies to PNs, with a minimum of 20 procedures per year required[46]. In addition to the minimal volume standards, there is an ongoing nationwide discussion regarding the centralisation of cancer care in general and renal cancer specifically. The discussion was prompted by the publication of the *Integraal Zorgakkoord* (IZA) in 2022[47]. This national healthcare agreement was initiated by the government with the aim of reorganising healthcare to improve efficiency, quality and accessibility.

PROspective Renal Cell Carcinoma cohort (PRO-RCC)

There is ongoing research in the field of localised, locally advanced and metastatic RCC and many questions are still unanswered and await further research. For this purpose, the Dutch PROspective Renal Cell Carcinoma cohort (PRO-RCC) is founded. Within this infrastructure, clinical data, patient reported outcomes measures (PROMs) and patient reported experience measures

(PREMS) are prospectively collected. To date, 25 hospitals in the Netherlands participate in PRO-RCC.

The PRO-RCC data collection is embedded in the framework of the Netherlands Cancer Registry (NCR). The NCR is a population-based cancer registry with nationwide coverage since 1989 and is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). Well-trained data managers extract data from the electronic patient files of newly diagnosed patients with cancer. Standard NCR items collected from all newly diagnosed renal cancer patients include patient- and tumour characteristics, disease stage, and first-line treatment. Vital status is recorded and updated each year based on annual linkage with the Municipal Personal Records Database which contains information on the vital status and emigration of all Dutch inhabitants. For patients enrolled in PRO-RCC, in addition to the standard NCR items, information concerning laboratory tests, complications/toxicity, specific details regarding systemic therapy and follow-up concerning disease recurrence and progression are collected as well (for a complete overview of items see http://iknl.nl/nkr/registratie/itemsets).

The infrastructure enables observational research in a real-world population on the long-term. The number of prospectively included patients will gradually increase over the years. To provide the opportunity to investigate research questions in the short term, PRO-RCC has collected clinical data from a historical cohort of patients diagnosed with metastatic RCC in 2018, 2019 and 2020. This cohort is used in several studies described in this thesis, together with standard available data from the NCR.

Aims and outline of this thesis

Analysis of various aspects of kidney cancer care can be used to gain valuable insights for clinical practice and to improve RCC care. The primary aim of this thesis was to evaluate kidney cancer care with nationwide real-world evidence on treatment and outcomes.

In light of the ageing population, the impact of developments in RCC treatment for older patients is a critical area of investigation. There is an increasing demand for personalised treatment strategies that consider patient age, comorbidities and general health. In **Chapter 2**, we examine trends in RCC incidence, treatment patterns, and relative survival rates in older versus younger

patients over time, in order to identify age-related disparities. In **Chapter 3,** we analyse the variation in clinical management of T1 RCC over time by surgical hospital volume and investigate the adherence to the minimal surgical volume standards of hospitals performing surgeries for RCC in the Netherlands. In **Chapter 4**, we evaluate whether upfront cytoreductive nephrectomy improves overall survival in patients with metastatic RCC who receive IO, in comparison to patients who receive TKI. During the writing of this thesis, the COVID-19 pandemic put a strain on healthcare with subsequent downscaling of regular healthcare. Therefore, we assess the impact of the COVID-19 pandemic on RCC care in the Netherlands which is described in **Chapter 5**. **Chapter 6** provides insights into the use and uptake of immunotherapy in routine clinical practice in the Netherlands since its approval. In **Chapter 7,** changes in predefined primary endpoints of clinical trials and their transparency are assessed, as significant changes in endpoints may bias the potential effect of the intervention. Finally, **Chapter 8** provides a description of the aims and infrastructure of the PRO-RCC study cohort. Details on the clinical data collection and patient-reported outcome measures are provided, as well as possibilities for future studies. **Chapter 9** provides a general discussion of all studies described in this thesis and specific recommendations based on the findings of these studies are formulated. In addition, future perspectives and opportunities are discussed.

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2

Trends in Treatment and Survival of Older versus Younger patients with Renal Cancer between 2011-2022

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Abstract

Objectives

To evaluate trends in management and survival of renal cell carcinoma (RCC) in older patients, given an aging population and ongoing diagnostic and therapeutic advancements.

Patients and Methods

Patients with RCC (2011-2022) were identified from the Netherlands Cancer Registry and grouped as <70 (younger), 70-79 (septuagenarians), ≥80 (octogenarians). Age-standardised incidence rates, treatment patterns and relative survival ratios with 95% confidence intervals (95%CI) were analysed by disease stage and age group.

Results

A total of 31,591 patients (54% younger, 31% septuagenarians, 15% octogenarians) were included. The incidence of T1a RCC significantly increased, especially in octogenarians. Conservative management (active surveillance and watchful waiting) was increasingly used over time, particularly among octogenarians with T1a RCC (65% to 83%). In advanced RCC (T4/N+/M+), most octogenarians received best supportive care (from 75% to 80% in recent years), while in the younger age categories patients shifted towards active treatments, particularly systemic therapy. Five-year relative survival decreased significantly in octogenarians with T1a RCC, from 86% (95%CI 77-95) to 71% (95%CI 59-82), but stabilised in other age groups. In advanced RCC, three-year relative survival improved from 26% (95%CI 24-29) to 41% (95%CI 38-44) in younger patients and from 19% (95%CI 16-22) to 25% (95%CI 22-29) in septuagenarians, but this was not observed in octogenarians.

Conclusion

Considerable variation in RCC management and survival is observed across age groups, with age dependent differences also evident in time trends. Benefits of recent advances in systemic treatment were not seen in octogenarians compared to younger patients. Optimising outcomes will require treatment strategies tailored to age, including evaluation of biological age and frailty.

Introduction

The global incidence of renal cell carcinoma (RCC) has been increasing in recent decades and the highest incidence is observed in Western countries. Contributing factors include established risk factors, such as obesity, hypertension, smoking, chronic kidney diseases, combined with an ageing population and improved imaging techniques [1]. A further rise is expected in the coming decades, with an estimated increase from approximately 2,700 in 2019 to 3,600 in 2032 in the Netherlands [2].

Over time, the diagnosis and management of RCC has changed. Nephron-sparing surgery– partial nephrectomy (PN) if feasible–, is preferred for T1 tumours. Focal therapy (FT) (including cryoablation, microwave ablation and radiofrequency ablation) is recognised as a viable, less invasive treatment alternative, while active surveillance (AS) is a monitoring strategy used for selected patients with low-risk disease [3]. For larger localised tumours, radical nephrectomy (RN) remains the recommended treatment. The treatment landscape for metastatic RCC has changed significantly with the introduction of tyrosine kinase inhibitors (TKIs) (since 2006) and, more recently, modern immunotherapy (IO). Both have contributed to improved survival of metastatic RCC [4].

The natural history of RCC varies, with small renal masses (SRMs) growing slowly and having a low risk of progression to metastatic RCC [5]. AS has been shown to be safe for selected patients with SRMs, especially in elderly and comorbid patients [6]. While the European Association of Urology (EAU) guidelines provide specific recommendations for the management of SRMs in these populations, evidence for other RCC stages is limited [3]. Furthermore, granular survival data on older RCC populations across all disease stages is lacking. The heterogeneity of elderly patients concerning comorbidities, performance status and life expectancy complicates treatment decisions, risking over- or undertreatment. Given the ageing population and advancements in RCC management, insight into clinical management and outcomes across all RCC stages in older patients is essential to optimise clinical-decision making and improve care.

Therefore, the aim of this nationwide study was to evaluate stage-specific trends in incidence, treatment and survival of older versus younger patients with RCC in the Netherlands from 2011 to 2022.

Materials & Methods

Patient selection

All patients aged 18 years or older with newly diagnosed RCC from 1 January 2011 to 31 December 2022 were identified through the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that collects data through notifications from the automated nationwide network and registry of histo- and cytopathology (PALGA). It is further complemented by additional sources, including the National Registry of Hospital Discharge (covering both inpatient and outpatient discharges) and radiotherapy institutes, to ensure inclusion of patients without histological confirmation. After case notification, specialised registration data managers extract basic information from the medical records. Comprehensive data on patient and tumour characteristics, disease stage, first-line treatment and vital status were available. Vital status (alive/dead/emigrated) is updated annually through a linkage to the Personal Records Database and was current up to 31 January 2024.

Definitions

Patients were grouped by age at diagnosis: <70 years (younger), 70–79 years (septuagenarians) and ≥80 years (octogenarians). A cut-off age of 70 years was chosen because many oncological studies, including Society of Geriatric Oncology (SIOG) consensus recommendations, have used 70 as the threshold for older age and implementing geriatric assessment [7,8]. All tumours were staged according to the Tumour-Node-Metastasis (TNM) classification and grouped based on their clinical TNM: T1a, T1b, T2–T3 and T4 or N+ or M+ (T4/N+/M+).

Treatment of T1a and T1b RCC was categorised as PN, RN, FT, conservative management, or other. Treatment of T2–T3 RCC was categorised in the same way as for cT1 tumours, except that FT was not presented as a separate category, since FT is not considered a relevant treatment modality for these tumour stages. In the rare cases where FT was applied, it was classified under "other". Due to limitations in medical record data, AS and watchful waiting (WW) could not be differentiated; both were therefore grouped as 'conservative management'. Treatment of advanced RCC (T4/N+/M+) was categorised as nephrectomy, nephrectomy combined with systemic therapy, systemic therapy, and best supportive care (BSC). Patients who received metastasis-directed therapy without subsequent systemic therapy or surgery were classified as BSC. First-line systemic therapy was further categorised as IO (including IO/IO

and IO/TKI combinations), TKI, or other. For the evaluation of time trends, three periods were defined based on the year of diagnosis; 2011-2014, 2015-2018 and 2019-2022.

Statistical analyses

Age- and stage specific incidence rates (crude rate per 100,000 person years) were calculated and the Estimated Annual Percentage of Change (EAPC) with 95% confidence intervals (95%CI) were used to evaluate temporal trends in incidence [9]. Descriptive analyses were performed to evaluate stage distribution by age group. Clinical management over time was evaluated by age and stage group. In addition, the type of first-line systemic therapy was evaluated for advanced RCC diagnosed between 2019-2022 by age group.

Relative survival ratios with 95%CI were calculated as an estimation of cause-specific survival using the Ederer II method [10]. This method estimates relative survival as the ratio of the observed survival in the patient cohort to the expected survival of a comparable group from the general population, matched by sex, age, and calendar year derived from Statistics Netherlands [11]. Survival time was defined as the time between date of diagnosis to the date of death, date of emigration or date of last update of vital status (31 January 2024), whichever came first. The median follow-up time of all patients was 6.5 years (interquartile range (IQR): 3.8-9.6 years). Five-year relative survival ratios were calculated, except for advanced RCC, where we report three-year survival ratios due to an insufficient number of cases to provide reliable estimates over longer periods, particularly in the older age groups. All survival analyses were stratified by disease stage and age group.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

This study was approved by the Privacy Review Board of the NCR (24-00407).

Results

Cohort characteristics

A total of 31,591 patients were diagnosed with RCC in the Netherlands between 2011 and 2022. The median age at diagnosis was 68 years: 54% were classified as younger, 31% as septuagenarians and 15% as octogenarians. The proportion of patients older than 70 years increased over time, from 42% in 2011-2014 to

48% in 2019-2022 (p<0.001). Patient and tumour characteristics, stratified by age group, are summarised in Table 1.

Most patients were male across all age groups, though the proportion of females increased with age (p<0.001). Overall, 80% of diagnoses were histologically confirmed, with notable differences across age groups: 42% in octogenarians compared to 78% in septuagenarians and 92% in younger patients (p<0.01). Octogenarians were less often diagnosed with T1a RCC (30% vs. 34%, p<0.001) and more often with advanced RCC (29% vs. 23-24%, p<0.01) compared to younger patients.

Table 1. Patient and tumour characteristics of patients diagnosed with renal cell carcinoma (RCC) in the Netherlands between 2011-2022, stratified by age group.

	Age group		
	<70 N = 17308	**70-79** N = 9678	**≥80** N = 4605
Year of diagnosis, N (%)			
2011-2014	5499 (32)	2577 (27)	1366 (30)
2015-2018	5973 (34)	3286 (34)	1583 (34)
2019-2022	5836 (34)	3815 (39)	1656 (36)
Sex, N (%)			
Male	11716 (68)	6224 (64)	2597 (56)
Histological confirmation, N (%)			
Yes	15947 (92)	7595 (78)	1918 (42)
Histology*			
Clear-cell RCC	11019 (69)	5165 (68)	1280 (67)
Papillary RCC	1997 (13)	989 (13)	215 (11)
Chromophobe RCC	845 (5.3)	331 (4.4)	97 (5.1)
Sarcomatoid RCC	218 (1.4)	117 (1.5)	27 (1.4)
RCC, not otherwise specified	1472 (9.2)	752 (9.9)	224 (12)
Other	396 (2.5)	241 (3.2)	75 (3.9)
Clinical stage at diagnosis (TNM)			
T1a N0 M0	5943 (34)	3329 (34)	1371 (30)
T1b N0 M0	3706 (21)	2095 (22)	984 (21)
T2-T3 N0 M0	3300 (19)	1664 (17)	777 (17)
T4/N+/M+	3917 (23)	2354 (24)	1322 (29)
Unknown	442 (2.6)	236 (2.4)	151 (3.3)

* Only in patients with histological confirmation

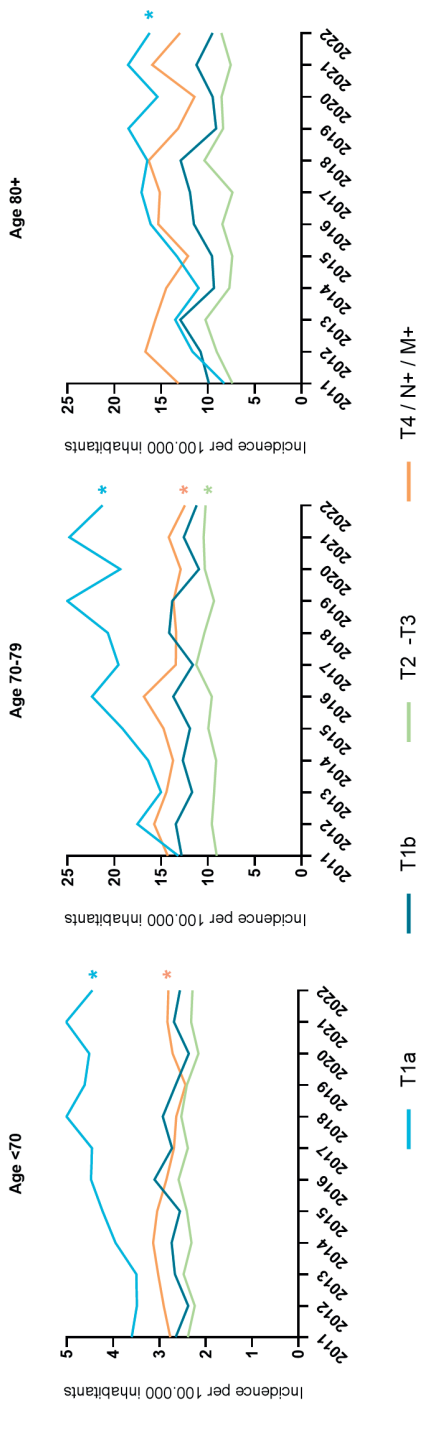

Figure 1. Age- and stage-specific renal cell carcinoma incidence rates (per 100,000 person years) between 2011-2022 in the Netherlands.
* Significant Estimated Annual Percent of Change (EAPC, see also supplementary Table 1).

Time trends in RCC

Figure 1 presents age and stage-specific incidence rates of RCC between 2011 and 2022, stratified by age group. Supplementary Table 1 shows the corresponding EAPCs with 95%CI. The most prominent trend over time is the significant increase in T1a RCC incidence across all age groups with EAPCs varying from 5.7% (95%CI 4.4-6.9) in octogenarians to 4.4% (95%CI 3.4-5.5) in septuagenarians and 3.1% (95%CI 2.5-3.7) in younger patients. In contrast, the incidence of T1b RCC and T2-T3 RCC remained largely stable across different age groups, although a slight increase was observed in septuagenarians with T2-T3 RCC (EAPC: 1.1%, 95%CI: 0.7-1.6). For advanced RCC small decreasing trends were observed across all age groups, although not statistically significant in octogenarians.

When evaluating stage distribution by age group over time, the proportion of T1a RCC increased across all age groups (from 30% to 37% in younger patients, 29% to 38% in septuagenarians, and from 23% to 35% in octogenarians). Conversely, advanced RCC diagnoses decreased (from 25% to 22% in younger patients, from 27% to 23% in septuagenarians, and from 31% to 27% in octogenarians) (Figure 2).

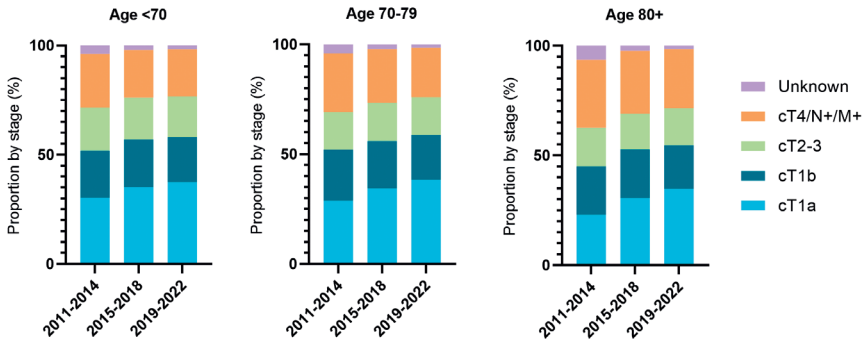

Figure 2. Stage distribution of renal cell carcinoma over time by age group.

Management of T1a RCC

The management of T1a RCC varied considerably by age, despite similar trends over time across age groups. Conservative management became increasingly common, while the use of RN and, to a lesser extent, PN declined. Among octogenarians, the vast majority (83%) were managed non-actively compared to 43% of septuagenarians and 19% of younger patients in the latest period (2019-2022). Among younger patients and septuagenarians receiving

active treatment, PN was the most commonly used treatment, followed by RN and FT (Figure 3a).

Management of T1b RCC

Changes in the management of T1b RCC were less distinct than those observed for T1a RCC. However, a shift toward more conservative approaches was evident, with younger patients and septuagenarians more often undergoing PN instead of RN, and octogenarians increasingly managed conservatively (47% in 2011-2014 versus 55% in 2019-2022), accompanied by a decline in RN (Figure 3b).

Management of T2-T3 RCC

No major changes in disease management of T2-T3 RCC over time were observed, except for a trend towards more conservative management, especially in octogenarians in recent years (36% to 42%). RN remained the mainstay of treatment regardless of age, with 52% of octogenarians undergoing RN in 2019-2022 compared to 85% of septuagenarians and 92% of younger patients (Figure 3c).

Management of T4/N+/M+ RCC

Over time, the use of systemic treatment (alone or in combination with nephrectomy) among octogenarians increased modestly (from 11% to 13%). In contrast, younger patients demonstrated a notable increase (from 49% to 58%), with a similar trend observed in septuagenarians (from 32% to 45%). Throughout the study period, the vast majority of octogenarians received BSC, with a slight increase over time (from 75 to 80%). A significant proportion of septuagenarians (39%) and younger patients (18%) also received BSC. The use of (cytoreductive) nephrectomy declined across all age groups (Figure 3d).

Among patients treated with systemic therapy during the 2019-2022 period, 79% of younger patients received IO or IO-based combinations as first-line therapy, while 21% were treated with TKIs. The use of IO decreased with age, being administered to 69% of septuagenarians and 48% of octogenarians (Supplementary Figure 1).

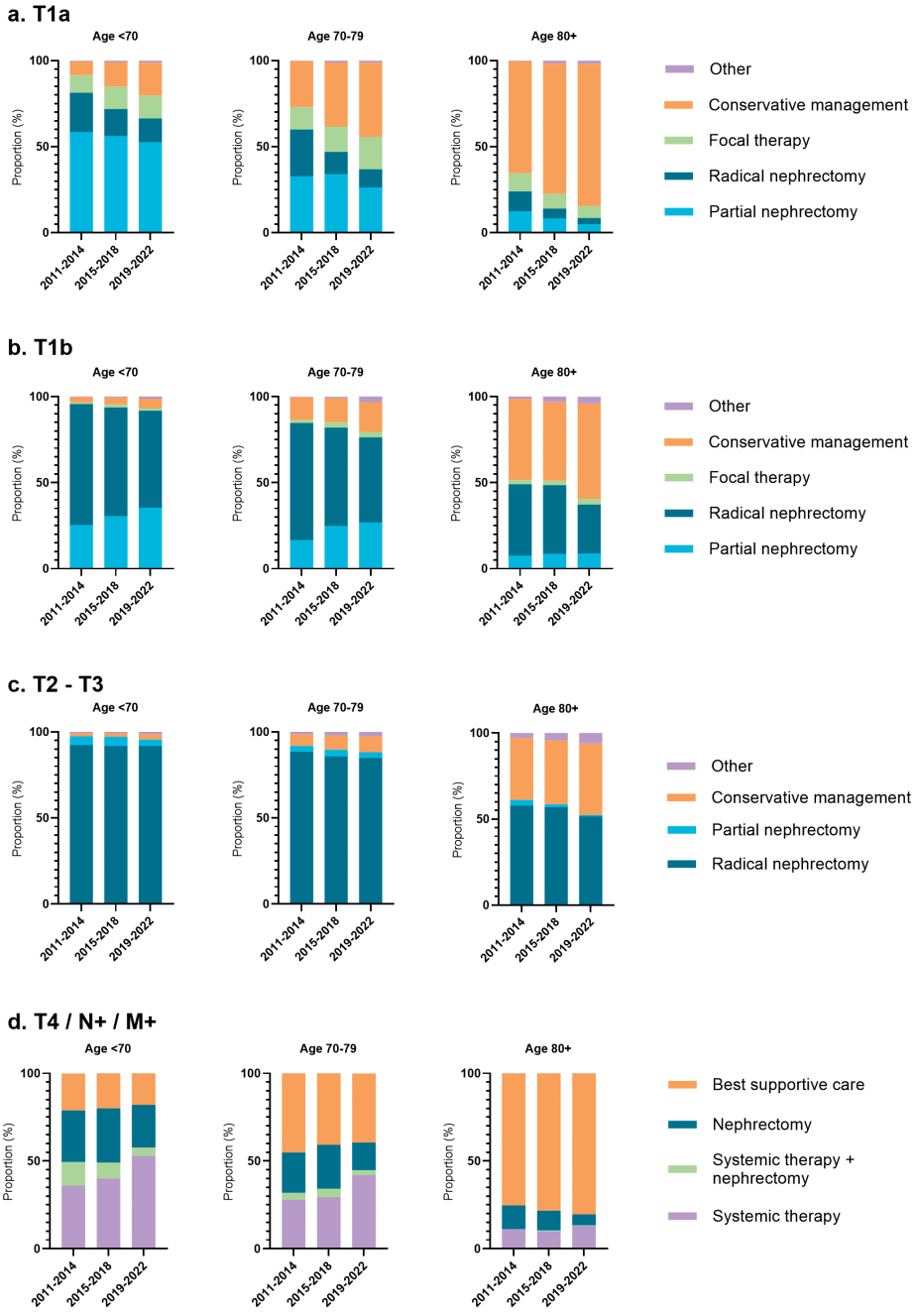

Figure 3. Treatment distribution of T1a (Figure 3a), T1b (Figure 3b), T2–T3 (Figure 3c), and T4/N+/M+ (Figure 3d) renal cell carcinoma over time by age group.

Relative survival

Five-year relative survival rates for T1a and T1b RCC remained largely stable over time across all age groups, except for a significant decline in octogenarians with T1a RCC from 86% (95%CI 77-95) to 71% (95%CI 59-82) (Figure 4 and Supplementary Table 2). Five-year survival rates for T2-T3 RCC improved modestly in younger patients and in septuagenarians but showed no change in octogenarians.

For advanced RCC, three-year relative survival increased markedly from 26% (95%CI 24-29) to 41% (95%CI 38-44) in younger patients, and modestly in septuagenarians (from 19% (95%CI 16-22) to 25% (95%CI 22-29)). However, this was not seen in octogenarians, with three-year relative survival rates of 12% (95%CI 8-16) in 2011-2014, 16% (95%CI 12-20) in 2015-2018, and 15% (95%CI 11-19) in 2019-2022.

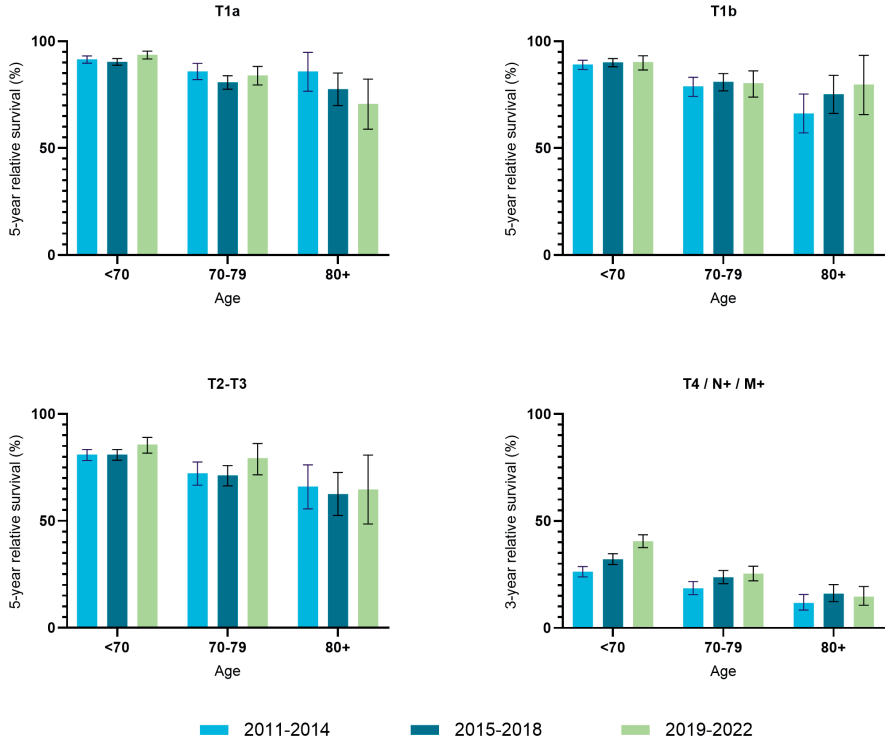

Figure 4. Relative survival rates by age groups and disease stage for patients diagnosed with renal cell carcinoma between 2011 and 2022 in the Netherlands. Five-year (T1a, T1b and T2/T3) rates and three-year (T4/N+/M+) rates with 95% confidence intervals are presented.

Discussion

In this nationwide study, we provided a comprehensive overview of age-specific differences in trends over time regarding the incidence, treatment and survival of RCC patients. A significant increase in the incidence of T1a RCC was observed across all age groups with the most notable rise in octogenarians. Conservative management became increasingly common for localised RCC across all age groups, with this trend being most pronounced in octogenarians with T1a RCC. For advanced RCC, the vast majority of octogenarians received BSC, with a slight increase over time. In contrast, systemic treatment was increasingly utilised among younger patients and septuagenarians. Five-year relative survival for T1a and T1b RCC remained stable, except for a significant decline in octogenarians with T1a RCC during the latest period. A modest improved survival was observed in younger patients and in septuagenarians with T2-T3 RCC, but not in octogenarians. Similarly, survival in advanced RCC improved for younger patients and septuagenarians but showed no significant change in octogenarians.

Our findings reflect the ageing population, as the proportion of patients aged >70 years has increased relatively more compared to those aged <70 years. The notable rise in T1a tumours is most likely due to the increased use of abdominal imaging and subsequent incidental detection [3].

Octogenarians were more often diagnosed with advanced RCC, which may be explained by the asymptomatic nature of the disease. As RCC frequently grows silently and is often detected incidentally, it is plausible that tumours in older patients have had more time to progress before diagnosis. Assuming a similar average age of tumour onset across patients, a diagnosis at age 80 compared to age 70 implies that the tumour had an additional decade to grow and progress before detection, potentially resulting in a more advanced disease stage at diagnosis. There was a clear decrease in the proportion of histologically confirmed tumours with increasing age, probably because elderly patients were more often managed conservatively.

The shift towards less invasive management for T1a RCC, especially in octogenarians, aligns with the EAU guidelines [3]. Consistent with our findings, Miller et al. [12] reported a rise in the use of minimally invasive treatments and conservative management among octogenarians with stage 1 RCC in the US between 2004 and 2015.

AS is a viable strategy, particularly for elderly and/or more comorbid patients with SRMs, given the low metastatic risk (1-2%) and the high comorbidity-related mortality [5,13]. FT has a lower risk of complications compared to PN while demonstrating comparable rates of metastatic progression and cancer mortality, despite higher rates of local recurrences [14,15]. This is particularly relevant for elderly, who are at increased risk of postoperative complications, even with advanced techniques such as robot-assisted surgery [16,17]. In more recent years, stereotactic body radiation therapy (SBRT) on the primary tumour is gaining acceptance as minimally invasive approach [18].

While conservative management for T1b and T2-T3 RCC increased across all age groups, most younger patients and septuagenarians still underwent active treatment. In contrast, conservative management was increasingly adopted in octogenarians, despite EAU guidelines recommending it specifically for T1a RCC and advocating partial/radical nephrectomy for larger tumours. A recent systematic review showed that PN is safe for older patients, and age alone should not be the sole reason for excluding them from this treatment option [19]. The observed shift towards increased use of conservative management in older patients is probably because they often present with more comorbidities and increased frailty, both of which favour non-surgical approaches. Frailty is associated with a higher risk of perioperative complications, increased readmission rates, and longer hospital stays [20]. Furthermore, deciding on surgery for elderly and frail patients remains complex and often requires thorough discussion in multidisciplinary team meetings [21].

A study of non-metastatic muscle-invasive bladder cancer showed that patients aged ≥75 years were significantly less likely to receive curative treatment. Factors contributing to not receive curative treatment were worse performance status, worse renal function, and prior abdominal/pelvic radiotherapy. Moreover, interhospital variation in treatment decisions was greatest among patients aged ≥75 years [22]. Similar clinical considerations may also influence the management of elderly patients with RCC.

An increase in systemic therapy use was observed across all age groups. However, octogenarians predominantly received BSC, with a slight increase over time, likely due to concerns about morbidity and shorter life expectancy. When first-line systemic therapy was used in octogenarians, TKIs were preferred, whereas IO was favoured in younger patients. Despite limited data on the safety and efficacy of IO in elderly [23], as they are often under-represented or excluded

from randomised controlled trials [24], studies suggest that carefully selected elderly patients may benefit from these treatments [25,26]. The absence of clear criteria for identifying suitable candidates complicates recommendations, potentially leading to physician and patient hesitation regarding these treatments.

The survival analysis revealed several key findings. Octogenarians with T1a RCC showed a decline in survival over time, in contrast to stable survival rates among septuagenarians and younger patients. The decline in survival among octogenarians with T1 RCC may be explained by an increasing proportion being found in patients who are less fit or have significant comorbidities. These patients generally have a lower life expectancy independent of their cancer diagnosis. However, this remains speculative and further research is needed to better understand these survival patterns in elderly patients. Additionally, while younger patients and septuagenarians with advanced RCC showed significant improvements in survival, octogenarians did not experience similar gains. These improvements in survival among younger age groups are most likely attributable to the introduction and increased use of novel systemic therapies in recent years [4]. These findings raise concerns about potential undertreatment and the limited impact of new therapies in this age group. Although some elderly patients may still benefit from surgery or systemic therapies, frailty and comorbidities complicate clinical decision-making [1,23]. Incorporating frailty assessments into shared decision-making could help balance the risks of overtreatment and undertreatment in this vulnerable population [27].

Our findings underscore the need for tailored guidelines for RCC management in elderly and to refine clinical decision making. While current guidelines recommend considering AS for elderly and comorbid patients with T1a tumours, clear selection criteria are lacking and no specific recommendations exist for larger tumours. Addressing these knowledge gaps is essential to ensure individualised, optimal treatment strategies for this growing patient population. Furthermore, evidence on frailty among patients with RCC is still relatively scarce, and the latest EAU guidelines did not provide any recommendations on frailty assessment [3,20]. Recent studies have shown that a standardised geriatric assessment can help oncologists identify whether older patients are frail or not [28]. Incorporating frailty assessments into clinical decision-making would enable more tailored treatment strategies, taking tumour-related factors and the patient's overall health status into consideration [20,27].

Overall, this study provides a comprehensive overview of trends in the management of RCC using nationwide data. Comprehensive, population-based overviews like ours remain scarce, as most existing studies focus on selective patient populations. By presenting descriptive statistics, we aim to describe trends and discuss potential explanations, while acknowledging that no causal inferences can be made. It offers valuable insights for clinical practices based on European guidelines, but certain limitations should be considered. The incidence of T1a RCC may be slightly underestimated because of ambiguity in clinical practice. Renal masses with uncertain behaviour (benign versus malignant) are not registered as RCC. As a result, some early-stage RCC cases may be missed if a definitive diagnosis is not established in clinical care.

Furthermore, the lack of data on comorbidities, frailty, and performance status limits our ability to evaluate their influence on treatment and survival trends, as well as to accurately assess biological age, which is a more precise indicator of overall health [29]. Due to limitations in medical record data, AS and WW could not be differentiated and they were therefore grouped as 'conservative management'. As previously mentioned, SBRT is becoming more widely accepted. However, within the time frame of the study, its use was still uncommon. Consequently, we were unable to present numbers. Finally, the COVD-19 pandemic may have slightly impacted treatment strategies in the most recent period, with AS being used more frequently, as demonstrated in a previous study. However, alternative management strategies were limited and relatively temporary during this period [30].

Conclusion

Management and survival of RCC varied significantly across age groups. Benefits of recent advances in systemic treatment were not seen in octogenarians compared to younger patients.

There is a need for tailored guidelines for RCC management in elderly patients, a growing patient population that is understudied and complex. Incorporating and assessment of comorbidities and frailty could help to optimise treatment strategies.

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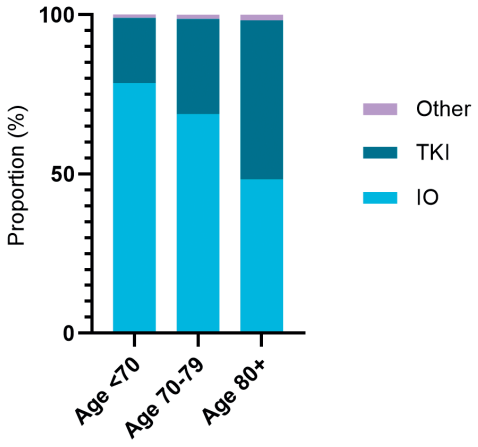
Supplementary material



Supplementary Figure 1. Distribution of type of first-line systemic treatment in systemically treated patients with T4/N+/M+ renal cell carcinoma (2019-2022).

Supplementary Table 1. Age- and stage-specific Estimated Annual Percent of Change (EAPC) with 95% Confidence Intervals (95% CI).

	EAPC	95% CI
Age <70		
T1a	**3.1%**	**2.5 – 3.7**
T1b	0.01%	-0.6 – 0.6
T2-T3	-0.3%	-0.7 – 0.1
T4/N+/M+	**-0.9%**	**-1.4 – -0.4**
Age 70-79		
T1a	**4.4%**	**3.4 – 5.5**
T1b	-0.6%	-1.3 – 0.1
T2-T3	**1.1%**	**0.7 – 1.6**
T4/N+/M+	**-1.3%**	**-1.9 – -0.7**
Age 80+		
T1a	**5.7%**	**4.4 – 6.9**
T1b	-0.5%	-1.5 – 0.6
T2-T3	0.01%	-1.0 – 1.0
T4/N+/M+	-0.8%	-1.8 – 0.2

Supplementary Table 2. Relative Survival ratios with 95% confidence intervals over time by age group.

Clinical stage at diagnosis (TNM)	<70 years			70-79 years			≥80 years		
	2011-2014	2015-2018	2019-2022	2011-2014	2015-2018	2019-2022	2011-2014	2015-2018	2019-2022
	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)	RS (95%CI)
T1a (5-year RS)	91.5% (89.7%-93.1%)	90.4% (88.8%-91.9%)	93.7% (91.7-95.4%)	85.9% (82.0%-89.6%)	80.8% (77.5%-83.9%)	84.0% (79.5%-88.2%)	85.9% (76.6%-94.8%)	77.6% (69.9%-85.1%)	70.7% (58.9%-82.3%)
T1b (5-year RS)	89.1% (86.8%-91.1%)	90.1% (88.0%-91.9%)	90.3% (86.5%-93.2%)	78.9% (74.2%-83.1%)	81.0% (76.8%-84.9%)	80.4% (73.9%-86.1%)	66.2% (57.1%-75.3%)	75.2% (66.2%-84.0%)	79.8% (65.7%-93.4%)
T2-3 (5-year RS)	81.0% (78.2%-83.4%)	81.0% (78.4%-83.4%)	85.7% (81.7%-89.0%)	72.3% (66.7%-77.5%)	71.3% (66.4%-75.9%)	79.4% (71.5%-86.2%)	66.0 % (55.6%-76.2%)	62.5% (52.5%-72.6%)	64.7% (48.5%-80.8%)
T4/N+/M+ (3-year RS)	26.3% (23.9%-28.7%)	32.1% (29.6%-34.7%)	40.5% (37.5%-43.5%)	18.5% (15.5%-21.7%)	23.7% (20.7%-26.9%)	25.4% (22.0%-28.9%)	11.7% (8.4%-15.6%)	16.0% (12.3%-20.3%)	14.6% (10.6%-19.4%)

RS: Relative Survival; CI: Confidence interval

3

Variation in the Management of cT1 Renal Cancer by Surgical Hospital Volume: A Nationwide Study

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Abstract

Objectives

To analyse variation in clinical management of cT1 renal cell carcinoma (RCC) in the Netherlands related to surgical hospital volume (HV).

Materials and methods

Patients diagnosed with cT1 RCC during 2014-2020 were identified in the Netherlands Cancer Registry. Patient- and tumour characteristics were retrieved. Hospitals performing kidney cancer surgery were categorised by annual HV as low (HV <25), medium (HV 25-49) and high (HV >50). Trends over time in nephron-sparing strategies for cT1a and cT1b were evaluated. Patient, tumour and treatment characteristics of (partial) nephrectomies were compared by HV. Variation in applied treatment was studied by HV.

Results

Between 2014-2020, 10,964 patients were diagnosed with cT1 RCC. Over time, a clear increase in nephron-sparing management was observed. The majority of cT1a underwent a partial nephrectomy (PN), although less PNs were applied over time (from 48% in 2014 to 41% in 2020). Active surveillance (AS) was increasingly applied (from 18% to 32%). For cT1a, 85% received nephron-sparing management in all HV categories, either with AS, PN, or focal therapy (FT). For T1b, radical nephrectomy (RN) remained the most common treatment (from 57% to 50%). Patients in high volume hospitals underwent more often PN (35%) for T1b compared to medium HV- (28%) and low HV (19%).

Conclusion

HV is related to variation in the management of cT1 RCC in the Netherlands. The EAU guidelines have recommended PN as treatment for cT1 RCC. In most patients with cT1a nephron-sparing management was applied in all HV categories, although differences in applied strategy were found and PN was more frequently used in high HV. For T1b, high HV was associated with less appliance of RN while PN was increasingly used. Therefore, closer guideline adherence was found in high volume hospitals.

Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers diagnosed worldwide[1,2]. In the Netherlands, the incidence of RCC has risen from approximately 1,500 cases per year in 2000, to more than 2,600 cases per year in 2020[3]. Widespread use of imaging has led to the increase in the incidence of small renal masses (renal tumours ≤4 cm) in the last decade, now representing 40-50% of all new patients with RCC[4,5]. Partial nephrectomy (PN) has evolved as a standard treatment for cT1 tumours, although alternative nephron-sparing strategies are also used for cT1a tumours, such as active surveillance (AS) and focal therapy (FT). For cT1 tumours PN is the preferred treatment. However, when PN is considered risky in frail patients or when technically not feasible, radical nephrectomy (RN) is an alternative if the contralateral kidney has a normal renal function[6].

A nationwide audit performed by the British Association of Urologic Surgeons (BAUS) between 2012 to 2016 demonstrated an association between annual hospital volume (HV) and the proportion of cT1 tumours treated with PN rather than RN (from 18.1% in centres performing <25 cases/year [lowest volume] to 61.8% in centres performing ≥100 cases/year [high volume]). This association persisted after adjustment for PADUA complexity. Furthermore, data from the BAUS audit revealed an inverse association between HV and complication rates for PN and RN[7].

In the Netherlands, Aben *et al.* described trends in Dutch RCC care between 2010 and 2014[8]. They found that most renal cancer patients in the Netherlands were treated according to guidelines and observed a clear increase in PN over the years. In addition, variations between HV and hospital status (university hospitals, large general hospitals and community hospitals) became apparent.

Although post-operative mortality is low, PN is recognised as a complex procedure with increased perioperative risk, such as bleeding, compared to RN[9,10] . In 2018, the Dutch Association of Urology (NVU) introduced the Dutch Volume Standard (DVS) in order to stimulate quality for hospitals performing PN and RN[11]. According to the DVS, the minimum number of RNs is 10 per year, and for PNs at least 10 procedures per year are required, calculated as mean over a period of three years.

Our objective is to analyse clinical variation over time in the management of cT1 renal cancers in the Netherlands, and to investigate the adherence to the DVS of hospitals performing surgeries for RCC.

Materials and Methods

In this historic cohort study, all patients diagnosed with a cT1 RCC during 2014-2020 were identified in the Netherlands Cancer Registry (NCR), maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR is a population-based registry comprised of data on all newly diagnosed cancer patients in the Netherlands and has nationwide coverage since 1989. The main source of notifications of new cancers is the automated nationwide network and registry of histo- and cytopathology (PALGA). In addition, cases of non-pathology proven tumours are supplied to the NCR by the Dutch Hospital Data (DHD). After notification, independent and trained data managers routinely extract patient, tumour, and treatment-related characteristics from medical records in all Dutch hospitals. Topography and morphology is coded according to the International Classification for Oncology (ICD-O) third edition and disease stage according to the UICC Tumour-Node-Metastasis classification[12,13].

Treatment was categorised into 5 groups: RN, PN, FT, AS, and other. It was assumed that patients with cT1 RCC without active treatment entered an active surveillance protocol, and were therefore classified as AS. Furthermore, PN, FT and AS were considered as nephron sparing strategy. To allow comparison, hospital volume categories were based on the BAUS hospital volume categories[7]. It was not possible to use the exact BAUS hospital volume categories due to smaller number of cases in the Netherlands. Therefore, hospital volume categories were defined as follows: hospitals performing surgeries were grouped according to their annual number of (partial) nephrectomies and categorised in to low volume (1-25 nephrectomies/year), medium volume (25-49/year) and high volume hospitals (>50/year). Hospitals not performing surgeries for renal cancer were categorised as 'hospital not performing surgeries'.

Hospitals performing surgeries were also categorised according to the 2018 DVS for both RN and PN. For total number of RN, hospitals were categorised into 'not adhering to the DVS' (1-9 RN/year) and 'adhering to the DVS' (≥10 RN/year). For PN the threshold of the DVS is also set at 10 PN/year, but averaged over a 3-year period. For each hospital we calculated the average number of PNs over a 3-year period. The calculated average number of PNs was assigned

to the middle year of the 3-year time period. For the last year of our study (2020), we calculated the average over the last 2 years (2019 and 2020). As some hospitals stopped performing (partial) nephrectomies during the study period, they were categorised to the 'hospital not performing surgeries' category from the moment they stopped performing this type of surgery. Those hospitals who performed 1-3 PNs per year were additionally checked by data managers for verification of this low number.

Descriptive analyses were performed to provide insight into patient characteristics. Trends in treatment over time were evaluated for cT1a and cT1b tumours separately.

Treatment variations were evaluated for cT1a and cT1b tumours diagnosed in 2019-2020 (after the introduction of the DVS) in both the DVS and HV categories and in hospitals not performing surgeries. Treatment patterns were also evaluated of referred and non-referred patients separately, according to the DVS for total number of (partial) nephrectomies. Patients were categorised as referred when their hospital of diagnosis differed from the hospital where surgical treatment was performed. Furthermore, insight was obtained into the geographical distribution of cT1a tumours treated with focal therapy. This was done by using the patient's zip code at time of diagnosis in order to calculate the proportion of cT1a tumours treated with FT by province. The results by province were plotted in a geographical map for patients diagnosed between 2018-2020.

For surgically treated patients, descriptive analyses on patient and treatment characteristics were performed stratified by HV. Additional chi-squared tests for categorical data and Mann-Whitney U test for continuous variables were used to evaluate differences. The percentage and trend of RNs and PNs performed in hospitals that comply with the DVS was calculated per year. The current volume standards were introduced in 2018. To evaluate trends in centralisation, earlier years were also included in these analyses as a reference.

All analyses were performed using Stata statistical software package (version 16.0). P-value <0.05 was considered statistically significant. For this study approval was obtained by the Privacy Review Board of the Netherlands Cancer Registry (K22.143).

Results

In total 10,964 patients with cT1 renal cancer were diagnosed in the Netherlands between 2014 and 2020, of which 59.7% cT1a and 40.1% cT1b. T-substage of the cT1 tumour was unknown in 15 patients (0.2%). Median age at diagnosis was 68 years (IQR = 59 – 75). In total 7,120 (64.9%) patients were surgically treated of which 53.8% with PN and 46.2% with RN.

Trends in treatment over time

From 2014 to 2020 the majority of patients with cT1a RCC were treated with PN, although over the years the proportion of patients treated with PN decreased (from 47.7% in 2014 to 41.2% in 2020). An increase of AS was observed (from 18.0% in 2014 to 32.2% in 2020). Appliance of FT was stable during this study period for cT1a RCC and showed no change in 2020 compared to 2014 (±12%) (Figure 1).

For cT1b tumours, RN was the most common treatment, although the overall proportion of RN decreased (from 56.8% in 2014 to 49.7% 2020). A slight increased use of PN was observed for cT1b, from 23.0% to 26.7%. AS was also applied more frequently over the years, from 12.5% to 17.0%.

Treatment variations

Variation in applied treatment was evaluated by HV. For cT1a tumours approximately 85% was treated with nephron-sparing management, independent of the HV category. Although, differences in the applied nephron-sparing strategy were observed between hospitals. Patients diagnosed in low volume hospitals and in hospitals not performing surgeries underwent AS more frequently. Fewer patients were treated with PN in low (33.5%) and medium (39.0%) volume hospitals compared to high volume hospitals (46.8%). FT was applied in 10.4-14.8% of the patients and was mostly used in low volume hospitals. For cT1a, there was a percentage of patients treated with RN, approximately 12-13% in all HV categories (Figure 2).

For cT1b tumours, a higher proportion of patients diagnosed in high HV was treated with PN (34.9%) compared to medium- (28.0%) and low HV (18.9%). As a consequence, fewer patients underwent a RN (46.5% vs. 51.2% vs. 55.9% respectively). Patients diagnosed in hospitals not performing surgery (and referring patients to surgical hospitals) showed the lowest percentage of RN for cT1b (45.7%), but applied AS more often (25.9%) than PN (23.5%).

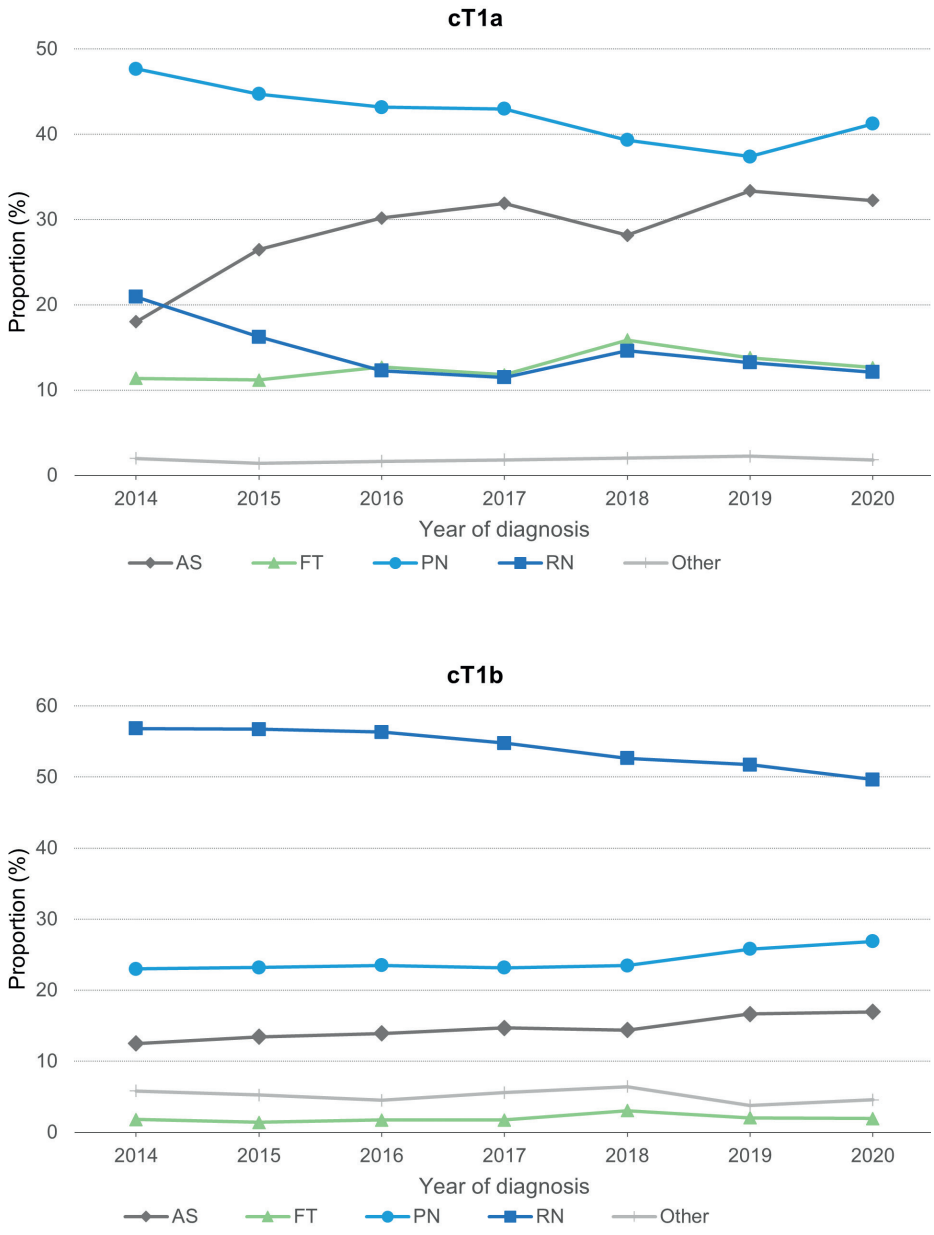

Figure 1. Distribution of treatment modalities over time (2014–2020) for cT1a and cT1b renal tumours.

Abbreviations: AS, active surveillance; FT, focal therapy; PN, partial nephrectomy; RN, radical nephrectomy.

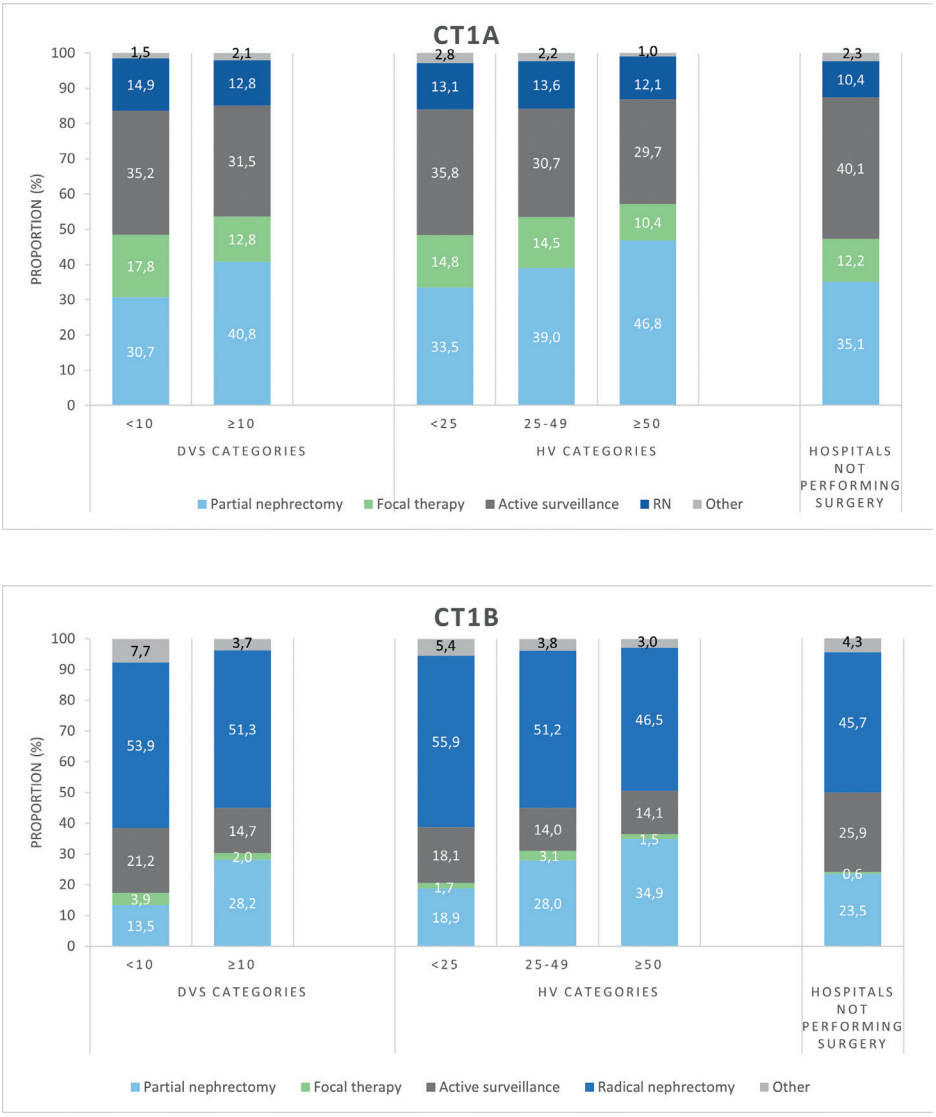

Figure 2. Treatment of patients diagnosed with cT1a and cT1b renal cell carcinoma (RCC) in 2019 and 2020 in the Netherlands. Applied management is shown in different categories: 1. Patients diagnosed in hospitals that adhere and not adhere to the DVS; 2. Patients diagnosed in three hospital volume categories (<25, 25–49, >50 surgeries per year); 3. Patients diagnosed in hospitals not performing surgeries.

Abbreviations: DVS, Dutch volume standard; HV, hospital volume.

Analysis of treatment patterns of referred and non-referred patients revealed that hospitals not adhering to the DVS referred patients mainly for PN while managing FT, AS and some RN in their own hospital. FT is not included in the DVS, but was evaluated in our study for referral patterns (Figure 3). In addition, geographical distribution showed large regional differences for patients that received FT for cT1a RCC, ranging from 1.4% to 24.5%, based on the zip code of the patient at the time of diagnosis (Figure 4).

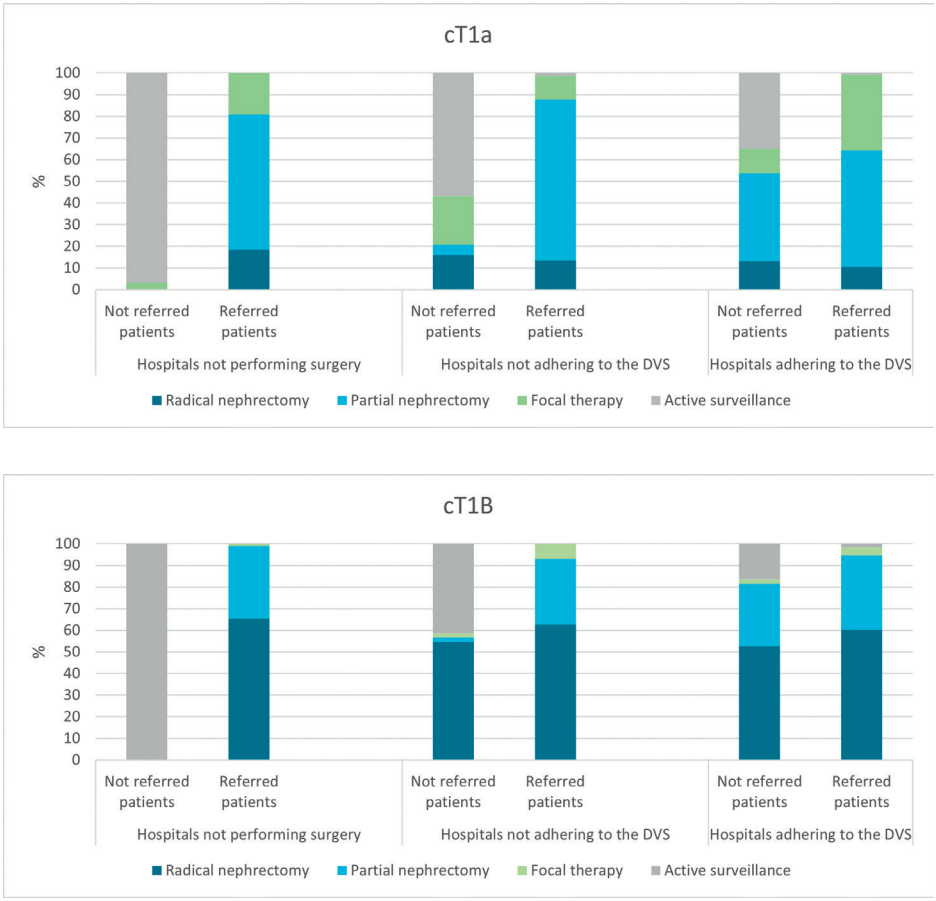

Figure 3. Referral patterns of patients diagnosed with renal cell carcinoma in 2019 and 2020 in hospitals not performing surgeries, hospitals not adhering to the DVS and hospital adhering to the DVS. (A) cT1a renal tumours. (B) cT1b renal tumours.

Abbreviations: DVS, Dutch volume standard

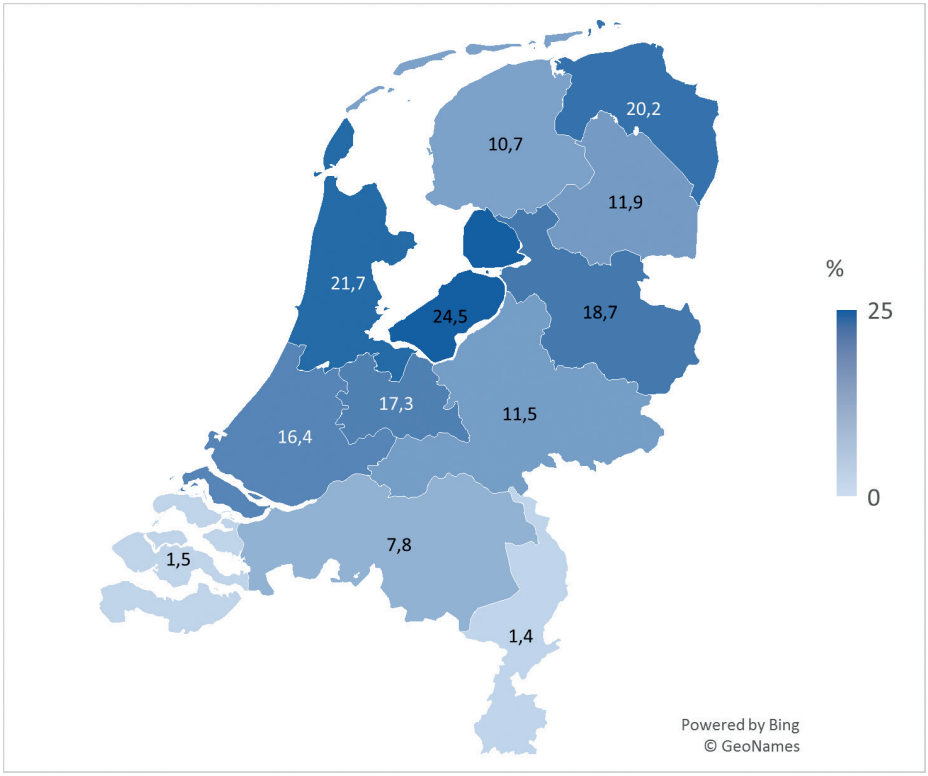

Figure 4. Geographical distribution of the proportion (%) of patients with cT1a renal cancer treated with focal therapy in the Netherlands in 2018–2020, based on the patients' ZIP code at the time of diagnosis.

Surgical treatment variation by HV

Surgically treated patients (PN or RN), diagnosed between 2014-2020, stratified by surgical HV (Table 1), showed that almost half of the patients had their (partial) nephrectomy in a medium volume hospital. High volume hospitals treated relatively more cT1a tumours compared to medium and low volume hospitals.

For cT1a, a higher proportion of patients was treated with PN in high vs. medium vs. low HV (83.0% vs. 74.5% vs. 65.0% respectively, p = <0.01). For cT1b, 43.1% of the patients underwent a PN in high HV, compared to 29.9% in a medium HV and 18.8% in a low HV (p = <0.01).

Furthermore, HV seems to be related to type of approach: Most (partial) nephrectomies in high volume hospitals were performed robot-assisted (67.0%), while in medium- and low volume hospitals the majority of (partial) nephrectomies were performed laparoscopically. In addition, low HV performed more surgeries with an open approach (27%), compared to 6.7% in high HV (p = <0.01).

Table 1. Characteristics of all surgically treated patients (*n* = 7120) diagnosed between 2014 and 2020 divided by surgical hospital volume category, and for cT1a and cT1b renal cell tumours.

Characteristic	Low HV <25 surgeries/ year N (%)	Medium HV 25-49 surgeries/ year N (%)	High HV >50 surgeries/ year N (%)	P-value
***N* cases**	1470 (20.7)	3504 (49.2)	2146 (30.1)	-
Gender				
Male	904 (61.5)	2210 (63.1)	1357 (63.2)	0.51*
Female	566 (38.5)	1294 (36.9)	789 (36.8)	
Median age at diagnosis (IQR)	66 (58-73)	65 (56-72)	64 (55-71)	<0.01**
Clinical substage				
cT1a	680 (46.2)	1795 (51.2)	1200 (55.9)	<0.01*
cT1b	789 (53.7)	1706 (48.7)	942 (43.9)	
Unknown	1 (0.1)	3 (0.1)	4 (0.2)	
Type of surgery				
PN	584 (39.7)	1845 (52.7)	1404 (65.4)	<0.01*
RN	886 (60.3)	1659 (47.3)	742 (34.6)	
Surgical approach				
Open	394 (26.8)	502 (14.3)	144 (6.7)	<0.01*
Laparoscopic	889 (60.5)	2080 (59.4)	521 (24.3)	
Robot-assisted	179 (12.2)	892 (25.4)	1437 (67.0)	
Unknown	8 (0.5)	30 (0.9)	44 (2.0)	

Table 1. *(Continued)*

Characteristic	Low HV <25 surgeries/ year N (%)	Medium HV 25-49 surgeries/ year N (%)	High HV >50 surgeries/ year N (%)	P-value
	T1a (n=3675)			
Type of surgery				
PN	435 (65.0)	1333 (74.5)	996 (83.0)	<0.01*
RN	245 (36.0)	462 (25.7)	204 (17.0)	
Surgical approach				
Open	211 (31.0)	276 (15.4)	69 (5.7)	<0.01*
Laparoscopic	364 (53.5)	930 (51.8)	201 (16.8)	
Robot-assisted	99 (14.6)	574 (32.0)	905 (75.4)	
Unknown	6 (0.9)	15 (0.8)	25 (2.1)	
	T1b (n=3437)			
Type of surgery				
PN	148 (18.8)	510 (29.9)	406 (43.1)	<0.01*
RN	641 (81.2)	1196 (70.1)	536 (56.9)	
Surgical approach				
Open	183 (23.2)	226 (13.3)	75 (8.0)	<0.01*
Laparoscopic	524 (66.4)	1147 (67.2)	319 (33.9)	
Robot-assisted	80 (10.1)	318 (18.6)	529 (56.1)	
Unknown	2 (0.3)	15 (0.9)	19 (2.0)	

Abbreviations: HV = Hospital volume, IQR = Interquartile range

* Chi-square test

** Mann-Whitney U test

Adherence to the Dutch Volume Standard

In total, 43 of 52 (82.7%) hospitals in 2020 did adhere to the DVS of at least 10 nephrectomies. For PN specifically, the number of hospitals performing PN adhering to the DVS was 26 of 42 in 2018 (61.9%), 25 of 42 in 2019 (59.5%) and 24 of 43 in 2020 (55.8%). Moreover, 19 hospitals in 2020 performed less than 10 partial nephrectomies.

The total number of RN and PN performed in a hospital adhering to the DVS is shown in figure 5. During the period 2014-2018, there was a trend of increasing proportion of PN performed in a hospital performing at least 10 PN per year (74.2% to 82.9%). After the introduction of the DVS in 2018, approximately 18% (17-19%) of the PNs was performed in a hospital not adhering to the DVS (Figure 5).

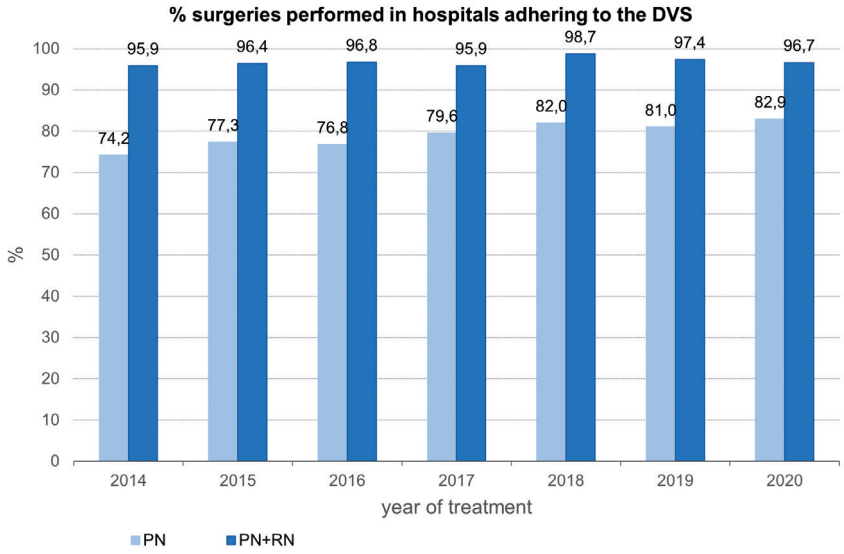

Figure 5. Proportion (%) of patients who underwent surgery that was performed in hospitals that adhere to the Dutch volume standard (DVS).

Abbreviations: PN, partial nephrectomy; RN, radical nephrectomy.

Discussion

This study shows that high volume hospitals showed closer guideline adherence compared to low- and medium HV for T1 RCC. The EAU guidelines have recommended PN as treatment for T1 RCC[6]. The majority of patients with cT1a RCC were treated with nephron-sparing options in all hospital categories, but variation in applied management was observed by HV showing increased numbers of PNs in high volume hospitals. For cT1b, there was an inverse correlation observed for RN and PN: the higher the HV, the lower the appliance of RN and more patients were treated with PN, suggesting closer guideline adherence. After the introduction of the DVS in 2018, still around 18% of PNs for cT1 tumours was performed in hospitals with an average of <10 PN annually.

Our results are in line with a previous audit from the BAUS[7]. In that study, Tran *et al.* analysed 13,045 surgically treated cT1 tumours between 2012 and 2016 in the United Kingdom. An association between HV and the proportion of cT1 tumours treated with PN rather than RN was found (also when subgrouping into cT1a and cT1b). This association persisted after adjustment for PADUA complexity. In

the BAUS data, 18% of the cT1a tumours was treated with PN in hospitals with a volume of <25 surgeries/year, compared to 37% in hospitals with a volume of 25-49 surgeries/year, and 51% in hospitals with a volume of 50-99 surgeries/year. Hospitals with a volume of ≥100 surgeries/year showed that 62% of the patients with cT1a were treated by PN. Our observations are in line with the BAUS analysis in the UK, as our analysis showed fewer usage of PN in low volume hospitals compared to medium and high volume hospitals. While the BAUS analysis was based on self-reported data, our data were retrieved from a nationwide registration, collected by trained and independent data-managers.

Another interesting finding of the BAUS audit was decreased complication rates with increasing HV for all patients, including patients treated with PN. PN is known to be a complex procedure and has been associated with higher complication rates compared to RN[9,14]. Other studies showed that undergoing robot-assisted PN at higher volume hospitals has been associated with decreased risk of conversion, positive surgical margins and complication rates[15,16]. Arora *et al.* analysed outcomes after any PN in the United States in relationship with HV and attempted to identify an optimal HV threshold for performing PN. They found that decreased complication rates were associated with increasing annual HV, with plateauing seen at 35 to 40 PN per year. In their study, robot-assisted PN showed a similar association, with plateauing seen at 18 to 20 PN annually[17]. In our study we could not analyse complication rates, as these data were not available. Future work should therefore be focused on a national registration of specialised care and surgery for RCC to improve clinical outcomes, decrease variations in practice patterns and subsequently increase guideline adherence in the Netherlands.

In an earlier study from the Netherlands, Aben *et al.* described guideline adherence for the management of cT1 RCC from 2010 to 2014[8]. An increase in PN of cT1a tumours and a clear trend of decreasing RN for cT1b tumours was observed over time. In addition, our study showed that the trend of decreased use of RN continued, although for cT1a tumours the use of PN decreased over time, whilst a clear increasing trend of AS was found. Furthermore, Aben *et al.* found that treatment in a high-volume hospital was associated with a higher probability of PN compared to RN for cT1a tumours. They hypothesised that referral from low- to high volume hospitals could partly explain the observed differences between low- and high- volume hospitals, although they did not analyse the referral patterns. Referral patterns in our study showed that hospitals not adhering to the DVS mostly referred patients for PN, whilst managing FT, AS

and some RN themselves. This could partly explain the observed difference between low- and high volume hospitals in usage of PN.

Another important observation in our study was the difference in surgical approach between different HV categories. Open nephrectomies were more common in low- and medium HV compared to high HV. The majority of the (partial) nephrectomies in high volume hospitals were performed robot-assisted. Laparoscopic RN is associated with less morbidity, shorter hospital stay and lower analgesic requirement compared to open RN[18]. Robot-assisted RN has not been proven superior over laparoscopic RN[19], although robot-assisted PN is associated with lower conversion rates to open surgery, shorter warm ischemia time, smaller change in post-operative GFR and shorter length of hospital stay compared to laparoscopic PN[20]. Robot-assisted PN has also shown superiority over open PN as well[21,22]. The question is however, if those surgeries performed open, could have been performed minimally invasive or if this was performed on specific indication. Without data of case-mix such as nephrometry-, or comorbidity scores supporting this open approach for RN for cT1 tumours in low volume hospitals we are unable to identify rationale behind open (partial) nephrectomies.

FT showed a stable usage of around 12% of the patients with cT1a tumours over time in the Netherlands. Interestingly, based on the zip code of the patient at the time of diagnosis, we found that in certain regions patients have better access to FT and that these data suggest less cross-regional referral from regions in which FT is not available.

An explanation for differences in type of nephron-sparing management applied in the different Dutch regions could be inadequate use of shared decision-making for cT1a RCC. T1 renal tumours are ideally suited for shared decision-making, as several treatment options are available with their pros and cons and should be discussed with the patient[23,24]. It would be interesting in future studies to analyse usage of shared decision-making correlated to HV.

Some limitations should be addressed. Case-mix data on tumour complexity (PADUA and/or RENAL score), patient comorbidity and complications were not available in the NCR and therefore these factors could not be taken into account in observed differences in treatment management between HV. Nevertheless, it is doubtful that low volume hospitals treated more complex tumours, as the BAUS data showed that in higher volume hospitals more complex PNs were

performed[7]. Nevertheless, this would be very interesting to analyse in future studies, as this could perhaps explain the differences found in management variation between hospitals.

In addition, despite that the registration was extracted by trained data-managers, some (partial) nephrectomies might have been missed during the registration. The missing registrations could have resulted in hospitals that are just below the threshold, although a limited effect of possible missing registrations is expected.

Also, in our analysis we did not include nefro-ureterectomies (for urothelial cancer) and surgeries for benign lesions, such as oncocytoma, as the definition of the DVS does specifically mention oncological surgeries for renal cell carcinoma. Hospitals might have taken these surgeries into account in their adherence to the DVS.

Lastly, it should be mentioned that the impact of the COVID-19 pandemic in 2020 was not evaluated in this study, which might have resulted in fewer PN's and could have prevented hospitals to reach the DVS threshold. The Dutch Association of Urology advised to delay surgery for cT1a low risk renal cell cancers during the COVID pandemic, and therefore it is possibly that PNs were postponed or treated otherwise.

Nevertheless, our study is based on a large nationwide registry with important information on differences in the management of cT1 RCC based on HV. We observed variation in applied management between different hospital categorisations. As fewer RNs were performed in high volume hospitals and PN was more often applied, it is questionable whether a volume standard with a minimum of 10 PN/year is adequate and therefore, an increase of the volume norms should be considered. With no data available on case-mix of cT1 tumours in the Netherlands, a nationwide registry could be the solution to further understand the current differences in the management of cT1 RCC in the Netherlands.

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4

A Nationwide Real-World Evaluation of Upfront Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma in the Immunotherapy Era

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Abstract

Background

Since the targeted therapy era, deferred cytoreductive nephrectomy (dCN) is offered to metastatic renal cell carcinoma (mRCC) patients who respond to systemic therapy. However, the transition to the current immunotherapy (IO) era necessitates a re-evaluation of cytoreductive nephrectomy in mRCC management.

Objective

To determine whether uCN improves overall survival (OS) in mRCC patients treated with IO compared to Tyrosine Kinase Inhibitor (TKI).

Design, setting, and participants

This nationwide historical cohort study included synchronous mRCC patients diagnosed in the Netherlands between 2018-2020 treated with IO/TKI. Propensity score-based inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier and Cox-regression analyses were used to adjust for prognostic differences. OS of patients with uCN was compared to those without. Analyses were stratified for IO and TKI.

Results and limitations

Of 872 patients, 433 received IO (63 uCN+IO versus 370 IO (± dCN)) and 439 received TKI (67 uCN+TKI vs. 372 TKI (± dCN)). Patients receiving uCN had more favourable prognostic factors compared to those starting with systemic therapy. In patients treated with IO, IPTW-adjusted median OS was 33 months for uCN+IO versus 24 months for IO (±dCN); HR 0.62, 95%CI 0.40-0.97. No significant difference in median OS was found in patients treated with TKI (19 months for uCN+TKI versus 17 months for TKI (±dCN); HR 0.76, 95%CI 0.52-1.12). Limitations include the observational nature and risk of residual confounding.

Conclusions

In the absence of RCTs, our results indicate a preference for uCN in mRCC patients with favourable prognostic factors in the IO era. Due to the risk of residual confounding, strong evidence from RCTs is needed.

Introduction

Cytoreductive nephrectomy (CN) was considered as the standard of care in patients with metastatic renal cell carcinoma (mRCC) in the cytokine era[1], based on two randomised controlled trials (RCTs) showing that upfront CN (uCN) with interferon improved overall survival (OS), compared to interferon alone[2,3]. The benefit of uCN was questioned in the targeted therapy era[1]. The CARMENA trial showed that sunitinib, a tyrosine kinase inhibitor (TKI), alone was not inferior to uCN followed by sunitinib in intermediate and poor risk mRCC patients[4]. The SURTIME trial investigated the optimal timing of CN. Synchronous mRCC patients were randomised to uCN followed by sunitinib or sunitinib followed by deferred CN (dCN) after 12 weeks in the absence of progression. The dCN group had a median OS of 32 months, significantly longer than 15 months in the uCN group[5]. Based on these results, uCN was no longer standard of care. Instead, patients responding to systemic therapy might be considered for dCN[6,7].

We have now entered the immunotherapy (IO) era. In the first-line most patients with mRCC are nowadays treated with a combination of immunotherapies (IO+IO) or with IO combined with TKI (IO+TKI), while TKI monotherapy is reserved for patients who cannot tolerate IO combinations, specific non-clear-cell RCC subtypes and favourable risk patients with clear-cell mRCC[8]. uCN may enhance IO efficacy by reducing tumour-derived immunosuppressive factors[9]. However, the exact role of CN in the IO era remains unclear. While RCT results are awaited, uCN continues to be performed in part of the patients, highlighting the need for more insight to guide clinical practice.

The aim of this study was to determine if uCN improves OS of patients with synchronous mRCC treated with IO compared to TKI, using real-world population-based data.

Material and methods

Patient selection

For this historic cohort study, all patients diagnosed with synchronous mRCC between 2018 and 2020 in the Netherlands were identified from the Netherlands Cancer Registry (NCR)[10]. Patients receiving IO or TKI within one year from diagnosis were included. Patients undergoing nephrectomy alone or best supportive care were excluded. Two separate cohorts were defined: the IO cohort (including IO-IO, IO-TKI, or IO monotherapy) and the TKI cohort. Within

each cohort, treatment arms were defined based on whether patients received uCN or not. The Privacy Review Board of the NCR approved this study (K23.239).

Clinical data and outcomes

The NCR contains data on patient and tumour characteristics, disease stage at diagnosis, initial treatment and vital status. For this study, the standard NCR data was expanded with data on comorbidities, performance status, laboratory tests (i.e. haemoglobin, creatinine, eGFR, platelets, neutrophils, calcium, albumin and LDH) and treatment details at diagnosis and during follow-up. Vital status is updated annually through the Personal Records Database, which holds information on vital status of all Dutch inhabitants. Topography and morphology were classified using the International Classification for Oncology (ICD-O) third edition and disease stage by the Union for International Cancer Control (UICC) Tumour-Node-Metastasis classification[11,12]. The International mRCC Database Consortium (IMDC) criteria were used to stratify patients into prognostic risk groups[13]. As only patients with synchronous mRCC who received systemic therapy within one year were included, none were considered favourable risk. The primary outcome was OS, defined as the time from initial treatment (nephrectomy or systemic therapy) to death or censoring (31 January 2023). For patients alive on 31 January 2023, median follow-up was 36 months (IQR 30-46).

Statistical analysis

Descriptive analyses provided insight into patient- and tumour characteristics. Multiple imputation by chained equations (MICE) was used to account for missing information[14]. Missing data were imputed 100 times and 500 bootstrap iterations determined standard errors and confidence intervals. We formulated two primary causal estimands for patients treated with IO and for patients treated with TKI; the marginal hazard ratio (HR) if all patients had been treated with IO (±dCN) versus if all patients had been treated with uCN+IO, and the marginal HR if all patients had been treated with TKI (±dCN) versus uCN+TKI. These estimands were calculated to assess whether uCN affects overall survival in patients with synchronous mRCC treated with either IO or TKI. Additionally, median overall survival was estimated for both scenarios. It is plausible that patient and tumour factors may influence the choice of treatment. To take differences between treatment arms within each subgroup into account, an inverse probability of treatment weighting (IPTW)-method based on propensity scores was used. The following covariates were included in the propensity score model: T-stage, N-stage, age, year of diagnosis, IMDC risk category, performance status (KPS ≥80 or <80), histology (clear-cell or non-clear cell),

number of metastatic sites (2 or ≥3), and the presence of lung, liver, brain or bone metastases. Propensity scores (i.e. the probability of having uCN versus first-line IO/TKI) were calculated for each patient by using a logistic regression model including all treatment-related factors. Weights were assigned to each patient based on the inverse of their propensity score, with higher weights assigned to those more likely to undergo one treatment but received the other. A density plot was graphed to assess the overlap of propensity score distributions. Standardised differences were calculated to evaluate the balance in covariates.

OS of treatment arms (with or without uCN) was compared using unadjusted and adjusted Kaplan-Meier curves. To approximate our estimands, we used IPTW-adjusted Cox regression analyses. Finally, we used a multivariate confounding score (MCS) to assess whether the observed associations were sensitive to unmeasured confounders[15] (Supplementary appendix A).

Statistical significance was defined as $p < 0.05$. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.1 with the packages *mice*, *survival*, *survminer, ggplot2, PSweight*.

Results

Patient and tumour characteristics

Between 2018 and 2020, 1517 patients were diagnosed with synchronous mRCC in the Netherlands. A total of 872 patients met the inclusion criteria, with 433 patients receiving IO and 439 receiving TKI (Figure 1). In the IO cohort, 63 patients received uCN with subsequent IO (uCN+IO) versus 370 patients received first-line IO, of which 12% (n=44) underwent dCN (IO (±dCN)). In the TKI cohort, 67 patients received uCN with subsequent TKI (uCN+TKI) versus 372 patients received first-line TKI, and dCN was performed in 4.6% (n=17) (TKI (±dCN)).

Patients receiving uCN differed significantly from patients with first-line IO/TKI in most baseline characteristics (Table 1). Patients treated with uCN had less extensive disease; less often T4 and/or N1 stage and fewer metastatic sites. Additionally, patients with uCN had better performance status and were more likely to be classified as intermediate risk rather than poor risk based on the IMDC score. Characteristics of patients before imputation are presented in Supplementary Table 1.

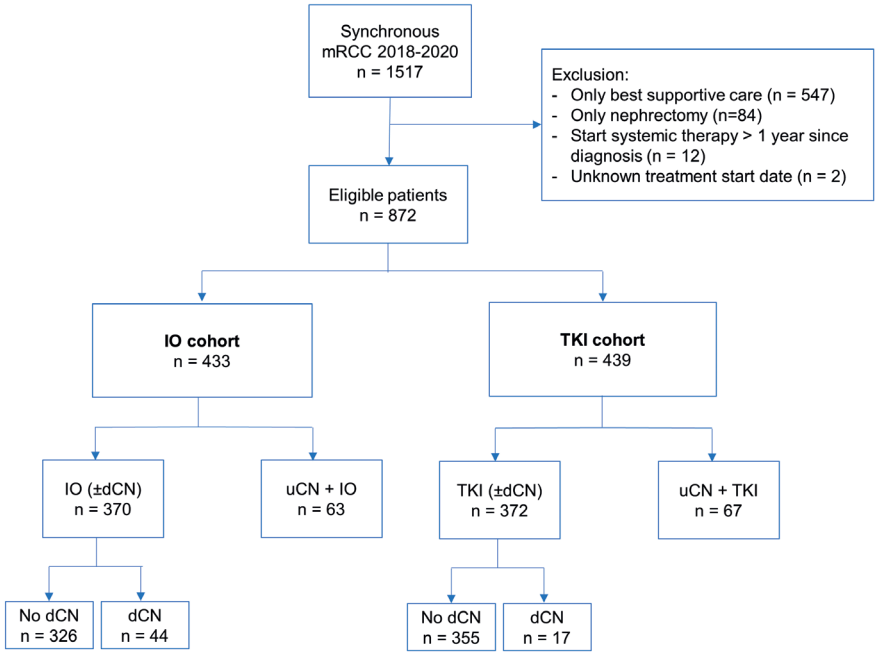

Figure 1. Flowchart of patient selection.

Abbreviations: mRCC, metastatic renal cell carcinoma; uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies; TKI, Tyrosine Kinase Inhibitors.

Figure 2 shows the distribution of the propensity scores with substantial overlap in the treatment arms in both the IO and TKI cohorts. After IPTW, all standardised differences decreased below 0.1, indicating successful balancing (Supplementary Table 2).

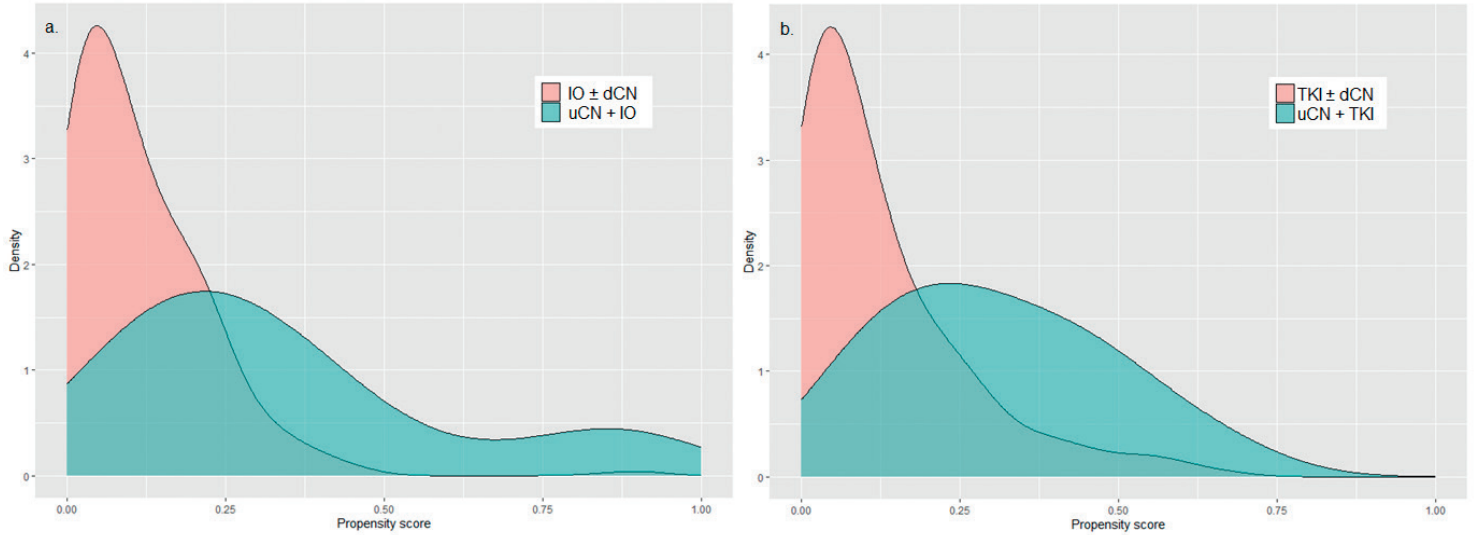

Figure 2. Distribution of the propensity scores in a. Subgroup IO and b. Subgroup TKI.

Abbreviations: uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies; TKI, Tyrosine Kinase Inhibitor

uCN and OS

In the IO cohort, IPTW-adjusted median OS was 33 months for uCN+IO versus 24 months for IO (±dCN) (Figure 3). 2-year OS was 63% (95%CI 51-76%) and 50% (95%CI 42-58%), respectively. The IPTW-adjusted Cox Regression yielded a HR of 0.62 (95% CI 0.40-0.97), indicating a significant probability of death in patients treated with uCN+IO. This was not observed in the TKI cohort (Figure 4). IPTW-adjusted median OS was 19 months for uCN+TKI versus 17 months for TKI (±dCN); HR 0.76, 95%CI 0.52-1.12. Two-year OS was 41% (95%CI 30-53%) and 36% (95%CI 23-46%), respectively. Unadjusted Kaplan-Meier curves of the IO and TKI cohorts are shown in Supplementary figure 1 and Supplementary figure 2. The interaction between type of systemic therapy and uCN was not significant (p=0.17).

The significant baseline differences and the inability to account for severity in patient and tumour characteristics highlight the risk of residual confounding. In a sensitivity analysis, we used the corrupted MCS to assess the potential effect of unmeasured confounders. A 10% increase in the corrupted MCS of patients receiving first-line IO (±dCN) would result in a non-significant treatment benefit of uCN. Given the mean MCS scores of 0.30 and 0.47 in the intermediate and poor risk subgroups, this would mean that 42% of intermediate risk patients would have to behave similarly to poor risk disease due to unmeasured confounders in order to have a non-significant treatment benefit of uCN in patients treated with IO (Supplementary Appendix A).

Table 1. Characteristics of patients (after imputations) for the IO cohort and the TKI cohort.

	IO cohort			TKI cohort		
	IO (± dCN) n = 370 (%)	uCN + IO n = 63 (%)	p-value[a]	TKI (± dCN) n = 372 (%)	uCN + TKI n = 67 (%)	p-value[a]
Year of diagnosis						
2018	5 (1.3)	12 (19)	**<0.001**	222 (60)	48 (72)	0.18
2019	176 (48)	28 (44)		75 (20)	10 (15)	
2020	189 (51)	23 (37)		75 (20)	9 (13)	
Age categories						
<60	107 (29)	16 (25)	0.4	90 (24)	17 (25)	0.2
61-70	141 (38)	28 (44)		126 (34)	17 (25)	
71-80	108 (29)	19 (30)		132 (36)	31 (46)	
81+	14 (3.8)	0 (0.0)		24 (6.4)	2 (3.0)	
Clinical T-stage						
cT1	71 (19)	15 (24)	**0.004**	82 (22)	13 (19)	**0.016**
cT2	123 (33)	17 (27)		122 (33)	24 (36)	
cT3	118 (32)	30 (48)		108 (29)	28 (42)	
cT4	58 (16)	1 (1.6)		60 (16)	2 (3.0)	
N-stage						**0.005**
N1	187 (51)	21 (33)	**0.012**	206 (55)	24 (36)	
Karnofsky Performance Score						
≥80	301 (81)	55 (87)	0.3	269 (72)	61 (91)	**0.001**
IMDC risk category						
Intermediate	205 (55)	44 (70)	**0.047**	206 (55)	45 (67)	0.097
Histology						
Clear-cell	305 (82)	52 (83)	>0.9	231 (62)	55 (82)	**0.001**
RCC NOS	50 (14)	6 (9)		78 (21)	2 (3.0)	
Non-clear cell	15 (4.1)	5 (8.0)		63 (17)	10 (15)	
Number of metastatic sites						
≥3	252 (68)	22 (35)	**<0.001**	262 (70)	29 (43)	**<0.001**
Lung metastasis	259 (70)	42 (67)	0.7	249 (67)	53 (80)	0.066
Liver metastasis	57 (15)	2 (3.2)	**0.016**	68 (18)	6 (9.0)	0.089
Bone metastasis	139 (38)	16 (25)	0.085	161 (43)	13 (19)	**<0.001**
Brain metastasis	23 (6.2)	1 (1.6)	0.2	22 (5.9)	0 (0.0)	0.082

a. Chi-square test

Abbreviations: uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies; TKI, Tyrosine Kinase Inhibitor; IMDC, International Metastatic renal cell carcinoma Database Consortium; RCC, renal cell carcinoma; NOS, Not Otherwise Specified.

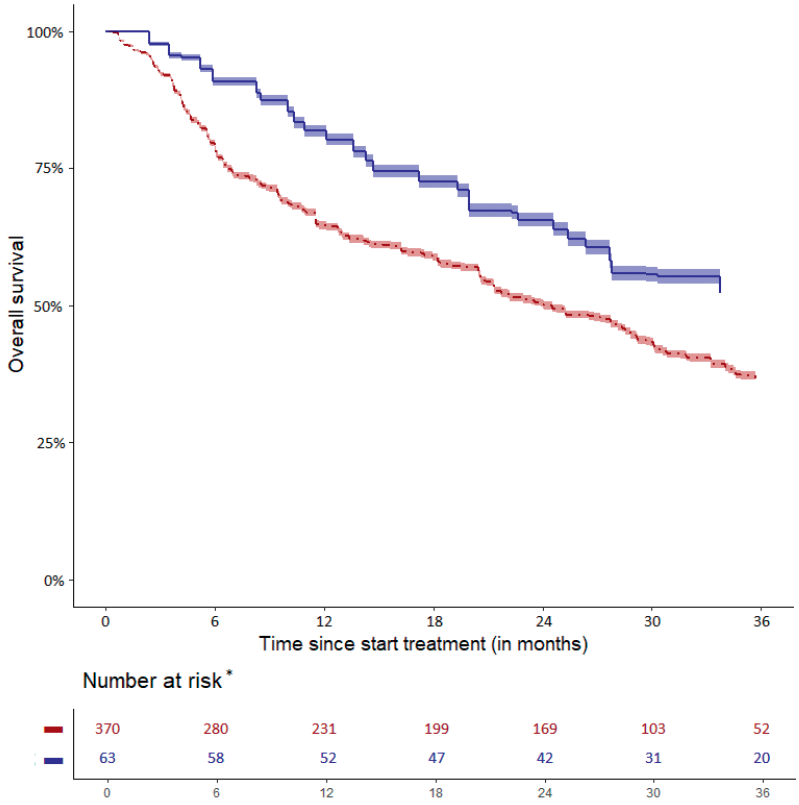

Figure 3. IPTW-adjusted Kaplan Meier overall survival estimates with 95%CI for Subgroup IO; uCN + IO (blue line) versus IO (±dCN) (red line).

Abbreviations: IPTW, Inverse Probability of Treatment Weighting; uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies.
*The unadjusted and pre-imputation 'Number at risk' table is shown.

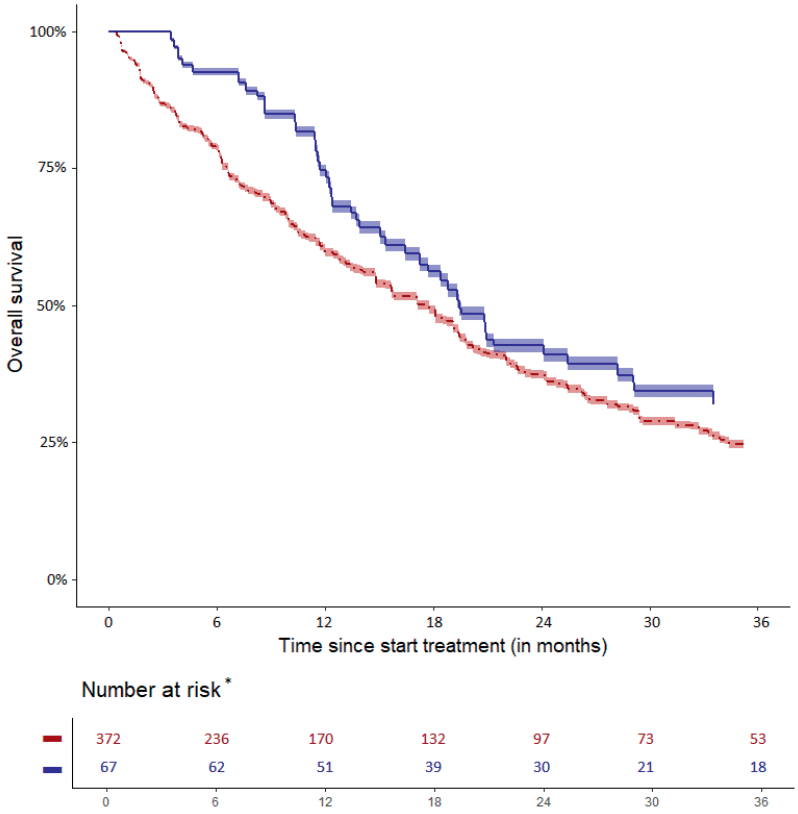

Figure 4. IPTW-adjusted Kaplan Meier overall survival estimates with 95%CI for SubgroupTKI; uCN + TKI (blue line) versus TKI (±dCN) (red line).

Abbreviations: IPTW, Inverse Probability of Treatment Weighting; uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; TKI, Tyrosine Kinase Inhibitor;
*The unadjusted and pre-imputation 'number at risk' table is shown.

Discussion

This study assessed whether uCN improves OS in patients with synchronous mRCC treated with IO compared to TKI, using real-world population-based data. Patients receiving uCN had more favourable prognostic factors compared to those starting with systemic therapy. After adjusting for these differences, median OS of patients with uCN in the IO cohort was 33 months versus 24 months for those without uCN (HR 0.62, 95% CI 0.40-0.97). However, in the TKI cohort, there was insufficient evidence to conclude a definitive survival benefit for patients treated with uCN versus no uCN (19 versus 17 months; HR 0.76, 95%CI 0.52-1.12).

The results observed in the TKI cohort of our study are in line with CARMENA[4]. No survival benefit was observed in patients treated with uCN followed by sunitinib versus sunitinib alone (median OS 16 versus 20 months; HR 0.97, 95%CI 0.79-1.19)[4]. SURTIME reported 15 months for uCN followed by sunitinib and 32 months for sunitinib followed by dCN[5]. Since these trials, uCN is no longer the standard of care. However, it is uncertain whether these results apply to the IO era.

In our study, we observed that patients treated with uCN in the IO cohort had a lower probability of death compared to those without, supporting the hypothesis that uCN is beneficial in the context of IO through the causal mechanism of tumour removal reducing immunosuppressive factors that might otherwise interfere with an effective immune response[9]. This is further supported by cases of spontaneous regression of metastatic lesions following nephrectomy[16], and recently strengthened by a post-hoc analysis of the JAVELIN-RENAL-101 trial which showed improved outcomes with avelumab+axitinib after uCN, but not with sunitinib following uCN[17]. However, no RCTs evaluate the role of uCN in the IO era[18,19], and only historical observational studies are available.

Our results are largely in line with the results of Ghatalia et al. who examined 1,907 synchronous mRCC patients between 2011 and 2020, identified from a United States nationwide database[20]. Of these, 58% received first-line systemic therapy (IO or TKI) and 42% uCN + systemic therapy. IO was used in 28% and 14% of each group, respectively. IPTW-adjusted OS was superior in patients receiving uCN + systemic therapy vs. first-line systemic therapy (27 vs. 15 months, p <0.001). However, they did not analyse IO and TKI separately.

Bakouny et al. also highlighted the potential benefit of uCN[21]. They evaluated 4,639 patients, diagnosed between 2009 and 2020, treated with IO (±9%) or TKI (±91%), with 2,560 receiving uCN. Separate survival analyses for IO and TKI showed a survival benefit in both cohorts for patients treated with uCN after IPTW-adjustment (balance was achieved for all included variables). However, as these patients were retrospectively selected from large academic centres, they are not necessarily representative of the general population, unlike our nationwide cohort. Additionally, both studies[20,21] mainly included patients treated with TKI, while our study, which focused on recent years, included 50% of patients receiving IO, allowing a more comprehensive evaluation of uCN in the IO era.

A recent multicentre study by Takemura et al. included patients treated with IO-based combinations. Multivariable analysis showed that CN (both upfront and deferred) was a favourable prognostic factor. However, they did not adjust for confounders[22].

Careful patient selection is crucial when considering uCN for mRCC. uCN is likely to be most beneficial in oligometastatic disease and in patients with low disease burden outside the primary tumour. A CARMENA subgroup analysis showed that patients with only one IMDC risk factor might still benefit from uCN, with improved OS observed in those receiving uCN compared to TKI alone[4]. Offering uCN to patients with low-volume disease who do not yet require systemic therapy is a viable strategy[6,23]. This approach does not delay the start of systemic therapy, which is particularly important for patients with extensive metastatic burden who may otherwise experience delay in receiving systemic therapy after surgery[24]. Primary tumour resection in selected patients may reduce tumour burden and delay progression[25]. Furthermore, Ditonno et al. found a lower 30-day postoperative complication rate after uCN compared to dCN[26].

Our analysis has several strengths. Firstly, it uses real-world data from a recent national cohort of unselected patients. After IPTW-adjustment, standardised differences indicated a negligible association (<0.1), indicating optimal balance of included confounders[27]. While imputation was required for performance status and IMDC risk category, multiple imputation techniques effectively address missing data[14,28,29]. To minimise selection bias, only patients treated within one year of diagnosis were included, reducing the risk of bias from including patients with indolent metastatic disease that did not require immediate treatment. Furthermore, data providing insight in the decision-making strategies regarding choice of systemic treatment were unavailable. Progression-free survival could not be evaluated, as follow-up regarding progression is not performed in a standardised way in general clinical practice and detailed data were not collected. Additionally, the optimal timing of CN was not evaluated.

Causal claims in this study most importantly rely on exchangeability ('no unmeasured confounding'), positivity and consistency. The latter two requirements mostly hold; all patients included in the study could have counterfactually been placed in the comparator treatment arm (positivity), and treating one patient does not affect the outcome of another patient

(consistency). There is likely some variation in the way treatment is given by different clinicians (also consistency), but this should have limited influence on marginal (population averaged) effect estimates. While we adjusted for a large number of potential confounding variables, some relevant unmeasured confounders remain, such as symptoms that could have influenced the choice for uCN (i.e. flank pain, severe haematuria). Symptomatic patients are more likely to receive uCN while having poor prognosis. We were also unable to adjust for severity of baseline characteristics and metastatic burden. However, as patients with uCN had more favourable prognostic factors, it is plausible that they were mostly asymptomatic, had low metastatic burden and less severe measured confounders[30]. This could positively bias the uCN arm compared to the first-line systemic therapy arm, as these factors have shown to predict first-year mortality after uCN in the recently developed SCREEN score[31]. To account for this, we performed a MCS-based sensitivity analysis. The benefit of uCN in IO-treated patients becomes unsignificant if 42% of the intermediate risk patients would behave similarly to poor risk due to unmeasured confounders, which is unlikely, but not impossible and consistent with the results of Bakouny et al[21]. The size of the causal estimate is in line with other studies[4,20,21].

Conclusion

In the absence of strong RCT evidence, our results indicate a preference for uCN in patients with favourable prognostic factors, such as low-volume (metastatic) disease. Our results can be used to guide clinical practice in the selection of patients for uCN in the IO era. Due to the risk of residual confounding strong evidence from RCTs is needed.

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Supplementary material

Supplementary Table 1. Characteristics of patients (before imputations) for Subgroup IO and Subgroup TKI.

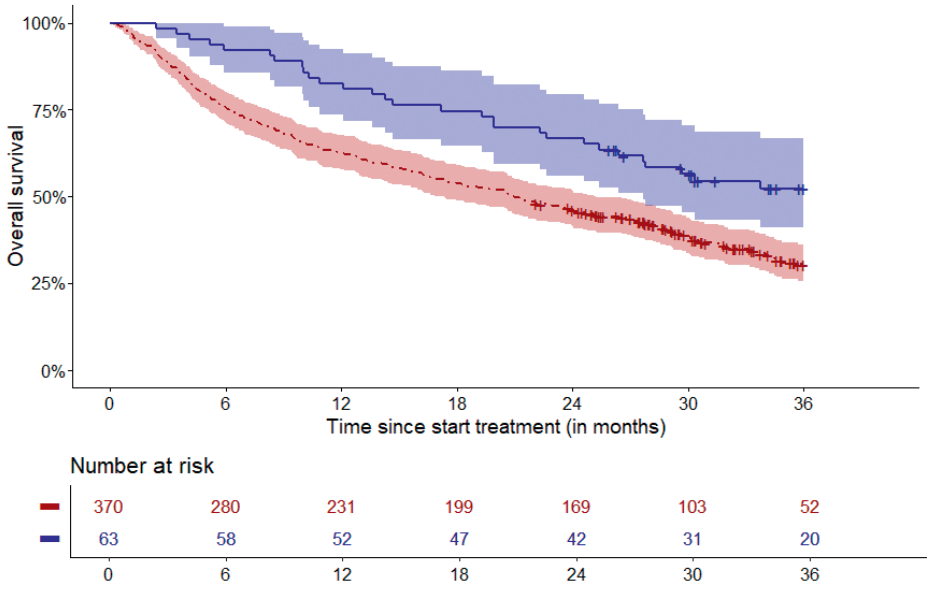
	IO cohort n = 433 (%)	TKI cohort n = 439 (%)
Year of diagnosis		
2018	17 (3.9)	270 (62)
2019	204 (47)	85 (19)
2020	212 (49)	84 (19)
Age categories		
<60	123 (28)	107 (24)
61-70	169 (39)	143 (33)
71-80	127 (29)	163 (37)
81+	14 (3.2)	26 (5.9)
Gender		
Male	317 (73)	314 (72)
Clinical T-stage		
cT1	81 (19)	92 (21)
cT2	134 (31)	141 (32)
cT3	142 (33)	131 (30)
cT4	56 (13)	58 (13)
Unknown	20 (4.6)	17 (3.9)
N-stage		
N0	212 (49)	194 (44)
N1	195 (45)	213 (49)
unknown	26 (6)	32 (7.2)
Karnofsky Performance Score		
≥80	285 (66)	248 (56)
<80	59 (14)	86 (20)
Unknown	89 (20)	105 (24)
IMDC risk category		
Intermediate	169 (39)	161 (37)
Poor	149 (34)	150 (34)
Intermediate/poor	115 (27)	128 (29)
Histology		
Clear-cell	357 (82)	286 (65)
RCC NOS	56 (13)	80 (18)
Non-clear cell	20 (4.6)	73 (17)
Number of metastatic sites		
≥3	274 (63)	291 (66)
Lung metastasis	301 (70)	302 (69)
Liver metastasis	59 (14)	74 (17)
Bone metastasis	155 (36)	174 (40)
Brain metastasis	24 (5.5)	22 (5.0)

Abbreviations: uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies; TKI, Tyrosine Kinase Inhibitor; IQR, interquartile range; IMDC, International Metastatic renal cell carcinoma Database Consortium; RCC, renal cell carcinoma; NOS, Not Otherwise Specified.

Supplementary Table 2. Standardised differences before IPTW (unweighted) and after IPTW (IPTW-weighted) for Subgroup IO and Subgroup TKI.

	IO cohort		TKI cohort	
	Unweighted	IPTW-weighted	Unweighted	IPTW-weighted
Age	0.3	0.026	0.2	0.045
Performance status	0.17	0.018	0.5	0.007
IMDC risk category	0.3	0.014	0.3	0.006
Histology	0.003	0.005	0.5	0.041
Number of metastatic sites	0.7	0.030	0.6	0.013
Year of diagnosis	0.6	0.050	0.3	0.084
T-stage	0.6	0.034	0.5	0.021
N-stage	0.4	0.028	0.4	0.022
Bone metastases	0.3	0.006	0.5	0.004
Lung metastases	0.072	0.009	0.3	0.005
Liver metastases	0.4	0.012	0.3	0.022
Brain metastases	0.2	0.046	0.4	0.001

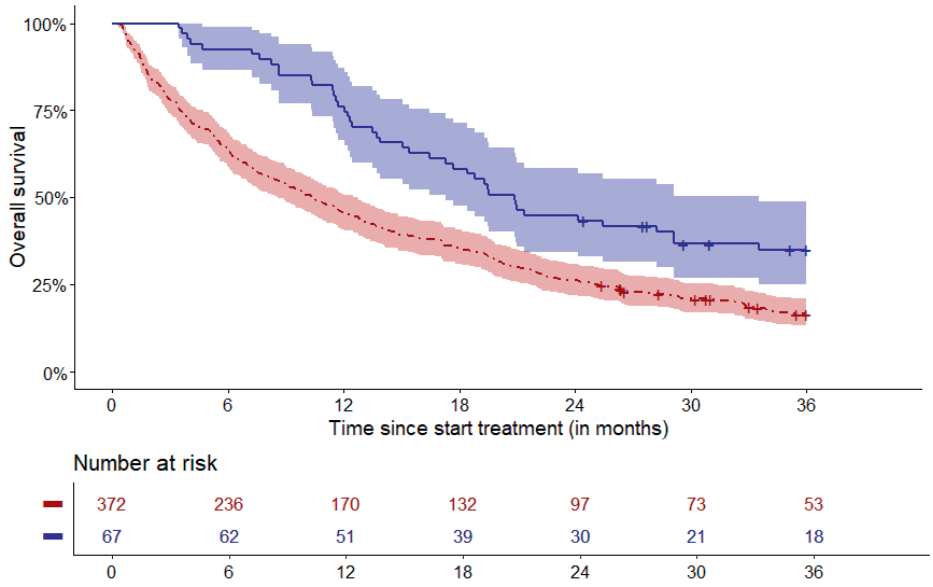
Abbreviations: IPTW, Inverse Probability of Treatment Weighting; IMDC, International Metastatic renal cell carcinoma Database Consortium; IO, immuno-oncology based therapies; TKI, Tyrosine Kinase Inhibitor.



Supplementary Figure 1. Unadjusted Kaplan Meier overall survival estimates with 95%CI for Subgroup IO; uCN + IO (blue line) versus IO (±dCN) (red line).

The unadjusted median OS of uCN+IO versus IO (±dCN) was 39 (95%CI 27-NE) versus 21 (95%CI 17-25) months, respectively (HR 0.44, 95%CI 0.26-0.73).

Abbreviations: uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; IO, immuno-oncology based therapies; OS, overall survival.



Supplementary Figure 2. Unadjusted Kaplan Meier overall survival estimates with 95%CI for Subgroup TKI; uCN + TKI (blue line) versus TKI (±dCN) (red line).

The unadjusted median OS of uCN+TKI versus TKI (±dCN) was 21 (95%CI 17-34) versus 10 (95%CI 9-12) months, respectively (HR 0.53, 95%CI 0.35-0.79).

Abbreviations: uCN, upfront cytoreductive nephrectomy; dCN, deferred cytoreductive nephrectomy; TKI, Tyrosine Kinase Inhibitor; OS, overall survival.

5

The Impact of the COVID-19 Pandemic on Renal Cancer Care

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Abstract

Purpose

To evaluate the impact of the COVID-19 pandemic on renal cell carcinoma (RCC) care in the Netherlands.

Methods

Newly diagnosed RCCs between 2018-2021 were selected from the Netherlands Cancer Registry; 2020-2021 was defined as COVID period and 2018-2019 as reference period. Numbers of RCCs were evaluated using three-week-moving averages, overall and by disease stage and age. Changes in treatment were evaluated with logistic regression analyses. To evaluate possible delays in care, time to start treatment was assessed. The cumulative number of metastatic RCC (mRCC) over time was assessed to evaluate stage shift.

Results

During the 1st COVID wave (week 9-22, 2020), the number of new RCC diagnoses decreased with 15%. Numbers restored partially in 2020, but remained 10% lower compared to 2018/2019. The decline was mostly due to a drop in T1a/T1b RCCs and in age>70 years. 2021 showed similar numbers to 2018/2019 without an increase due to previously missed RCCs. Treatment-related changes during the 1st COVID wave were limited and temporarily; less surgery in T1a RCCs in favour of more active surveillance, and in mRCC targeted therapy was preferred over immunotherapy. Time to start of first-line treatment was not prolonged during the 1st COVID wave. No increase in mRCC was found until the end of 2021.

Conclusions

The COVID-19 pandemic resulted in fewer RCC diagnoses, especially T1a/T1b tumours. Treatment-related changes appeared to be limited, temporarily and in accordance with the adapted guidelines. The diagnostic delay could lead to more advanced RCCs in later years but there are no indications for this yet.

Introduction

The COVID-19 pandemic was caused by a novel coronavirus (Severe Acute Respiratory Syncrome-coronavirus-2, or SARS-CoV-2) and put a strain on healthcare. The first COVID-19 positive patient in the Netherlands was diagnosed on February 27th 2020[1]. Evolving in the Southern part of the country, the virus spread gradually to the rest of the country. To prevent further spreading and overload in hospitals, a national lockdown was announced on March 23rd 2020. The increased number of hospitalised patients with a COVID-19 infection led to downscaling of medical care. All none-urgent appointments, procedures and treatments were postponed or cancelled. At the same time, patients who feared becoming infected or did not want to burden the healthcare system, avoided (urgent) medical care[2]. As a result, during the first COVID-19 wave a significant decrease of 25% in cancer diagnoses was reported in the Netherlands[2,3].

Adapted (inter)national guidelines were published to guide downscaling of regular care[4–7]. Specifically for renal cancers, the Dutch Urological Association (NVU) prioritised surgical treatments based on their urgency. Partial nephrectomies and focal therapies were considered less urgent and it was recommended to perform these procedures only if surgical capacity was available. The recommendation in Dutch guidelines for radical nephrectomies was not changed; perform surgery within six weeks[4]. The Dutch Association of Medical Oncology (NVMO) recommended to delay systemic therapy (in metastatic disease) if possible. Specifically for renal cancer, it was advised to cancel maintenance immunotherapy and to consider replacement of immunotherapy with targeted therapy (tyrosine kinase inhibitors)[7].

The impact of the COVID-19 pandemic and the subsequent downscaling of regular healthcare in the Netherlands on renal cancer care is largely unknown. Therefore, we aimed to evaluate this impact on the number of new renal cell carcinoma (RCC) diagnoses, age and disease stage and treatment. Also, the effect on surgical capacity in hospitals was evaluated.

Materials and methods

All patients newly diagnosed with renal cancer between January 2018 and December 2021 were identified through the population-based Netherlands Cancer Registry (NCR) and included in this historic cohort study[8]. Data on patient, tumour and treatment characteristics were extracted from the NCR.

Detailed description of the variables and used definitions are described in Appendix A.

Patients diagnosed in 2020 and 2021 were considered as the COVID cohort and patients diagnosed in 2018/2019 as the reference cohort. As the impact of the COVID-19 outbreak in general and specifically on clinical care was most prominent in 2020, we divided the year 2020 into four distinct time periods based on COVID-19 related public restrictions: Pre-COVID (week 1-8, 2020), 1st COVID wave (week 9-22, 2020; in week 9 the first COVID-19 patient was diagnosed in the Netherlands and in week 13 the first national lockdown started which ended in week 22), 2nd COVID period without lockdown (week 23-40 in 2020), 3rd COVID period with (partial) lockdown (week 41-52, 2020; the Netherlands experienced a period of different restrictions and (partial) lockdowns).

Descriptive analyses were performed to provide insight in the COVID cohort and the reference cohort. Three-week-moving averages were used to evaluate the number of new diagnoses in the COVID period versus the reference period. Due to small numbers, a 3-week moving average was used to evaluate trends over time, smoothing the average number per time period. In addition, the relative change in the number of diagnoses in 2020 and 2021 was evaluated by considering 2018/2019 as 100%. Logistic regression analyses were performed to evaluate age-adjusted probability of receiving a certain treatment and Mann-Whitney U tests were used to compare time since diagnosis to start treatment. A more detailed description of the statistical analyses is given in Appendix A. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Caroline, USA) and STATA version 16.1 software (StataCorp, College Station, Texas, USA). P-value <0.05 was considered as statistically significant.

Results

New RCC diagnoses

Patient- and tumour characteristics of the COVID cohort (divided in distinct periods) and the reference cohort were described in Table 1.

In Figure 1a and 1b, three week moving averages of new RCC diagnoses are presented for 2020 and 2021 with 2018/2019 as reference period. During the 1st COVID wave, an initial decline of 30% in RCC diagnoses was found, followed by decreased numbers up to 20% in subsequent periods. After week 38 short periods with increased numbers (up to 15%) were observed. Overall, the total

number of RCC diagnoses in 2020 remained 10% (N~270) lower than expected based on 2018/2019. In 2021 the number of new RCC diagnoses was comparable to 2018/2019.

Disease stage and age at diagnosis

Figure 2a (supplementary) shows that the observed decline in number of diagnoses in 2020 was largely due to a decline in T1a/T1b tumours (N~218); during the 1st COVID wave and the 2nd COVID period without lockdown, numbers were significantly decreased. In the 3rd COVID wave with (partial) lockdown, the number of new T1a/T1b tumours was still slightly lower, but this decline was not statistically significant. In other disease stages a small decline in numbers was observed as well, but altogether not statistically significant. In 2021 no clear differences in the number of diagnoses per disease stage were found (Supplementary Figure 3a).

In Figure 2b (supplementary) the incidence of RCC in 2020 was presented by age group; the decline in number of diagnoses was most prominent in elderly patients (>70 years) during the 1st COVID wave and the 2nd COVID period without lockdown. From week 41 in 2020 onwards the incidence was not statistically different to the reference years. In 2021 no significant differences in the number of diagnoses by age were found (Supplementary Figure 3b).

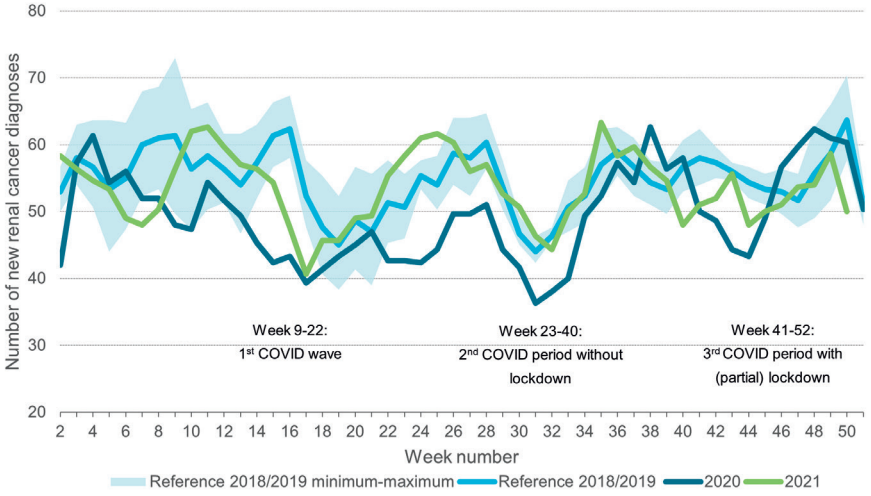
Table 1. Baseline characteristics of patients diagnosed with renal cancer in 2020 (divided in time periods), in 2021, and in the reference period 2018/2019.

	2018-2019	Pre-COVID: Week 1-8 2020	1st COVID wave: Week 9-22 2020	2nd COVID period without lockdown: Week 23-40 2020	3rd COVID period with (partial) lockdown: Week 41-52 2020	2021
Total number of patients, n (%)	5665 (100%)	407 (100%)	639 (100%)	862 (100%)	655 (100%)	2797 (100%)
Gender, n (%)						
Male	3719 (65.6)	279 (68.6%)	426 (66.7%)	565 (65.5%)	421 (64.3%)	1797 (64.2%)
Female	1946 (34.4)	128 (31.4%)	213 (33.3%)	297 (34.5%)	234 (35.7%)	1000 (35.8%)
Age at diagnosis						
Median (IQR)	69.0 (60.0-75.0)	68.0 (59.0-75.0)	67.0 (59.0-75.0)	68.5 (60.0-76.0)	70.0 (62.0-75.0)	68.0 (59.0-76.0)
Mean (SD)	67.3 (11.9)	67.1 (11.9)	66.8 (11.4)	67.5 (11.6)	68.0 (11.3)	67.3 (11.7)
Age at diagnosis, n (%)						
<60	1404 (24.8%)	107 (26.3%)	163 (25.5%)	206 (23.9%)	140 (21.4%)	714 (25.5%)
61-70	1563 (27.6%)	114 (28.0%)	197 (30.8%)	246 (28.5%)	186 (28.4%)	748 (26.7%)
71-80	1850 (32.7%)	135 (33.2%)	187 (29.3%)	284 (32.9%)	243 (37.1%)	948 (33.9%)
81+	848 (15.0%)	51 (12.5%)	92 (14.4%)	126 (14.6%)	86 (13.1%)	387 (13.8%)
Clinical tumor size at diagnosis (mm)						
Median (IQR)	50.0 (30.0-79.0)	48.0 (30.0-80.0)	50.0 (32.0-81.0)	50.0 (30.0-81.0)	51.0 (32.0-80.0)	50.0 (30.0-80.0)
Mean (SD)	58.0 (36.4)	57.1 *(35.2)*	59.8 (37.0)	58.6 (36.5)	59.0 (35.6)	58.2 (36.8)
M stage, n (%)						
M0	4656 (82.2%)	327 (80.3%)	516 (80.8%)	673 (78.1%)	532 (81.2%)	2272 (81.2%)
M1	1009 (17.8%)	80 (19.7%)	123 (19.2%)	189 (21.9%)	122 (18.6%)	520 (18.6%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	5 (0.2%)

Table 1. *(Continued)*

	2018-2019	Pre-COVID: Week 1-8 2020	1st COVID wave: Week 9-22 2020	2nd COVID period without lockdown: Week 23-40 2020	3rd COVID period with (partial) lockdown: Week 41-52 2020	2021
Disease stage (TNM), n (%)						
Stage 1	3309 (58.4%)	235 (57.7%)	348 (54.5%)	485 (56.3%)	369 (56.3%)	1612 (57.6%)
Stage 2	691 (12.2%)	51 (12.5%)	83 (13.0%)	101 (11.7%)	86 (13.1%)	327 (11.7%)
Stage 3	330 (5.8%)	21 (5.2%)	51 (8.0%)	47 (5.5%)	38 (5.8%)	166 (5.9%)
Stage 4	1236 (21.8%)	96 (23.6%)	145 (22.7%)	219 (25.4%)	150 (22.9%)	649 (23.2%)
Unknown	99 (1.7%)	4 (1.0%)	12 (1.9%)	10 (1.2%)	12 (1.8%)	43 (1.5%)
Morphology, n (%)						
No histological confirmation	1156 (20.4%)	79 (19.4%)	119 (18.6%)	191 (22.2%)	129 (19.7%)	562 (20.1%)
Clear Cell	2958 (52.2%)	195 (47.9%)	328 (51.3%)	442 (51.3%)	358 (54.7%)	1406 (50.3%)
Papillary	592 (10.5%)	49 (12.0%)	65 (10.2%)	83 (9.6%)	72 (11.0%)	313 (11.2%)
Chromophobe	232 (4.1%)	18 (4.4%)	30 (4.7%)	29 (3.4%)	26 (4.0%)	121 (4.3%)
Sarcomatoid	58 (1.0%)	1 (0.2%)	5 (0.8%)	3 (0.3%)	1 (0.2%)	11 (0.4%)
RCC NOS	511 (9.0%)	53 (13.0%)	77 (12.1%)	88 (10.2%)	57 (8.7%)	282 (10.1%)
Other	158 (2.8%)	12 (2.9%)	15 (2.3%)	26 (3.0%)	12 (1.8%)	102 (3.6%)

a.



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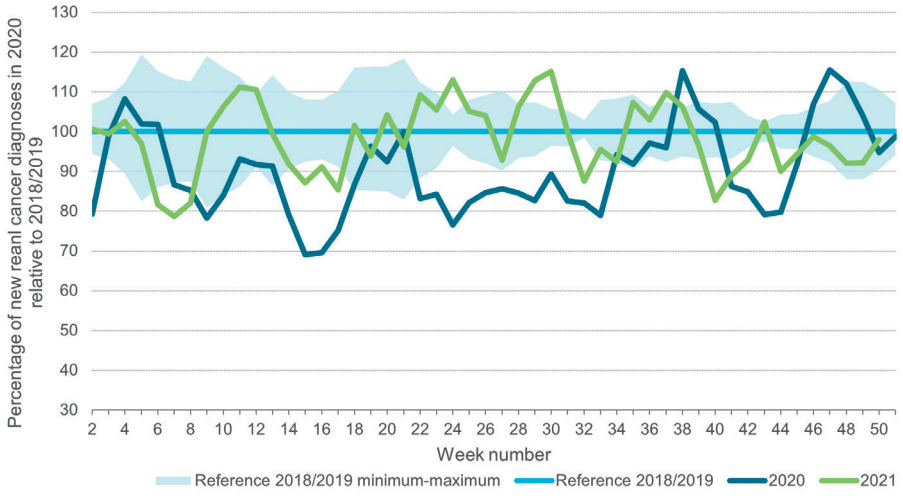

Figure 1. (a) Three week moving averages of newly diagnosed renal cancers (absolute numbers) in the Netherlands in 2020 and 2021 compared to the reference period 2018/2019 and (b) relative to the reference period.

Treatment

Patients with T1a RCC had more often no active treatment during the 2nd COVID period compared to 2018/2019 (36.2% versus 30.8%, OR 1.36, 95%CI 1.03-1.80) and less often underwent radical nephrectomy (9.6% versus 13.8%, OR 0.67, 95%CI 0.45-0.99) (supplementary Figure 4 and supplementary Table 2). In 2021, more often "Other treatment" was applied compared to the reference period. Patients with "Other treatment" mostly had radiotherapy. This increased use of radiotherapy is unlikely to be COVID-related but might reflect a new development in clinical practice for old and frail patients in the Netherlands. No other significant changes in treatment of T1a RCC were observed.

For T1b RCC no statistically significant differences were found in treatment per time period, except for "Other treatment", similar to the observation in T1a tumors. Also for T2/T3 RCC no statistically significant differences were observed.

Patients with T4 RCC and/or nodal involvement and/or metastatic disease had significantly more often immunotherapy and less often targeted therapy in all time periods of 2020 and in 2021 (only the OR for targeted therapy during the 1st COVID wave in 2020 was not statistically significant) compared to the reference period. The increased use of immunotherapy is probably not COVID-related as this was already seen pre-COVID. The temporary decline in use of immunotherapy and increased use of targeted therapy during the 1st COVID wave in 2020 reflects the recommendation to consider replacement of immunotherapy with targeted therapy (immunotherapy 29.0% in the 1st COVID wave vs. 31.3-33.3% in later periods and targeted therapy 20.7% in the 1st COVID wave vs. 11.4-15.6% in later periods).

Time to treatment

The median time from diagnosis to (partial) nephrectomy was on average 48 days in 2018/2019 and did not increase during the 1st COVID wave (46 days) and even decreased significantly in later periods (40-43 days, $p<0.01$). Concerning the start of first-line systemic therapy, median time from diagnosis to the start of first-line systemic therapy (significantly) increased from the 2nd COVID period onwards from 25 to 30-31 days (Supplementary Figure 5).

Surgical volume

During the 1st COVID wave an increase up to approximately 40% more (partial) nephrectomies per week was observed (supplementary Figure 6). This increase was followed by a similar decrease during the 2nd COVID period without

lockdown. However, overall a decline of 11% in (partial) nephrectomies was observed in 2020 (~1513 in 2020 and ~1694 in 2018/2019). In 2021 the number of (partial) nephrectomies were more in line with 2018/2019 (~1603 in 2021).

Stage shift over time

The cumulative absolute number of patients with metastatic disease in 2020 and 2021 was presented in Figure 7 (supplementary) to evaluate early effects of a delayed diagnosis. From May/June onwards in 2020 a small increase in the number of metastatic RCC diagnoses was observed, which falls within the expected range of the reference period. In 2020 and 2021 approximately 520 patients were diagnosed annually with metastatic RCC compared to approximately 500 in 2018-2019.

Discussion

The current study revealed that the outbreak of COVID-19 in the Netherlands caused an initial decline of 30% in the number of RCC diagnoses. Numbers restored partially, but remained 10% lower in 2020 as compared to 2018/2019. In 2021 numbers were largely similar to those of 2018/2019, but no subsequent increase in RCC diagnoses due to delayed diagnosis was observed. The observed decline was largely due to a decrease in T1a/T1b tumours and most pronounced among elderly. Up to 2021, no evidence of a stage shift towards more advanced RCC due to a diagnostic delay was found. Treatment related changes during the 1st COVID wave were limited and temporarily, and in adherence to adjusted guidelines[5,6].

Our analyses showed that the decrease in RCC diagnoses was most pronounced in older people, which is consistent with previous studies evaluating the impact of the COVID-19 pandemic on cancer care[9-11]. Especially elderly have avoided healthcare services due to their increased vulnerability to a COVID-19 infection, which can be more severe and fatal in this group[12]. The higher mortality rate associated with COVID-19 also might have led to a reduced number of RCC diagnoses, especially in older patients[12]. However, the impact of excess mortality due to COVID-19 on the number of bladder- and prostate cancer was minimal, estimating approximately 15 fewer cases of bladder- and 25 fewer cases of prostate cancer[9,11]. Therefore, we expect that the impact of the excess mortality on the number of RCC diagnoses is negligible.

As stated before, the decline in RCC diagnoses was mostly due to a drop in T1a/T1b tumours. It is known that the majority of small renal cancers are diagnosed incidentally on imaging modalities[13]. The downscaling of regular medical care and subsequent use of imaging during the COVID-19 wave might explain this observation[14,15]. Interestingly, no subsequent increase in diagnoses was seen; the number of diagnoses in 2021 was not higher than expected. Also, no increase in more advanced stage RCCs was found. These results are in line with the results of a small cohort study from Italy. They reported a decrease of 10% in the number of RCC diagnoses in 2020 compared to 2018-2019 (N~91 vs. 101), without evidence of a short-term trend towards advanced stage tumours in 2020[16]. Our hypothesis is that part of the patients who formerly had an incidentally detected renal tumour did not seek medical attention once their complaints/symptoms became self-limiting and they no longer required a visit to a health-care provider. On short term, it is not expected that this would lead to more advanced cancers, as small renal tumours have a slow growth rate[17]. However, on long term, delayed presentation of undiagnosed renal cancers could possibly lead to advanced stages and potentially impact survival[18].

Next to the impact of the COVID-19 pandemic on RCC diagnoses, we evaluated treatment-related changes. T1a RCC was more often managed with active surveillance and less often with surgery during the 2nd COVID period without lockdown in 2020. This might be explained by hospitals focusing on (catching up of) urgent (oncological) surgeries and T1a RCC can be managed with active surveillance postponing surgery. Following adapted treatment guidelines, less patients with T4 and/or N+ and/or M+ disease received immunotherapy during the 1st COVID wave and targeted therapy was applied more often. This observation is consistent with the outcome of an international online survey among physicians involved in the treatment of metastatic RCC who preferred targeted therapy over immunotherapy regimens, whereas prior to the pandemic, ipilimumab/nivolumab was the preferred choice in intermediate/poor risk patients[19]. The temporarily decreased use of immunotherapy might affect survival rates of patients with advanced RCC since long-term survival is better for patients with first-line combination immunotherapy than those treated with sunitinib[19-21].

Time to first-line systemic therapy was slightly prolonged following the 1st COVID wave. For patients with metastatic RCC, systemic therapy is initiated based on risk stratification, radiological progression, and/or symptomatic disease. Delaying systemic therapy for metastatic RCC has shown to have little impact

on overall survival, especially when there are limited metastases. Nevertheless, an optimal approach to select these patients has not yet been established[22]. After the COVID-19 outbreak, time to (partial) nephrectomy was not increased during the 1st COVID wave and even became shorter in the subsequent periods. In anticipation of a potential worsening of the COVID-19 situation, hospitals might have fully addressed waiting lists for oncological purposes. We observed that initially (during the 1st COVID wave) the number of nephrectomies was larger compared to what was expected based on the reference period. This is in line with findings from other studies[9,11,23]. A explanation might be that despite the reduced surgical capacity of hospitals during the 1st COVID wave, oncological surgeries were prioritised. In 2020, however, the total number of surgeries was slightly lower compared to previous years which might be the result of fewer diagnoses and the preference for other nephron sparing managements such as active surveillance and focal therapy, particularly for T1a/T1b RCC[24-26].

Although our study is based on a large nationwide registry, there are some limitations to be considered. Despite the use of nationwide data, some subgroup analyses were based on small numbers. Additionally, the reference period was defined as 2018/2019 and trends over time were not taken into account. However, we assume that this effect is minimal since the incidence of RCC was stabilising in recent years in the Netherlands. A slight underestimation of undiagnosed RCC cases cannot be excluded[27].

Conclusions

Overall, during the 1st COVID wave health care providers were able to provide RCC care in accordance with the adapted treatment guidelines in the Netherlands. A decline of approximately 10% in all RCC diagnoses was observed in 2020, mostly in T1a/T1b tumours and among elderly. No increase of RCC diagnoses in 2021 was found due to the decline in 2020. There was no evidence for more advanced stage disease until 2021. However, long-term consequences of a potential stage shift due to a diagnostic delay and its impact on the oncological outcomes should be assessed in future research.

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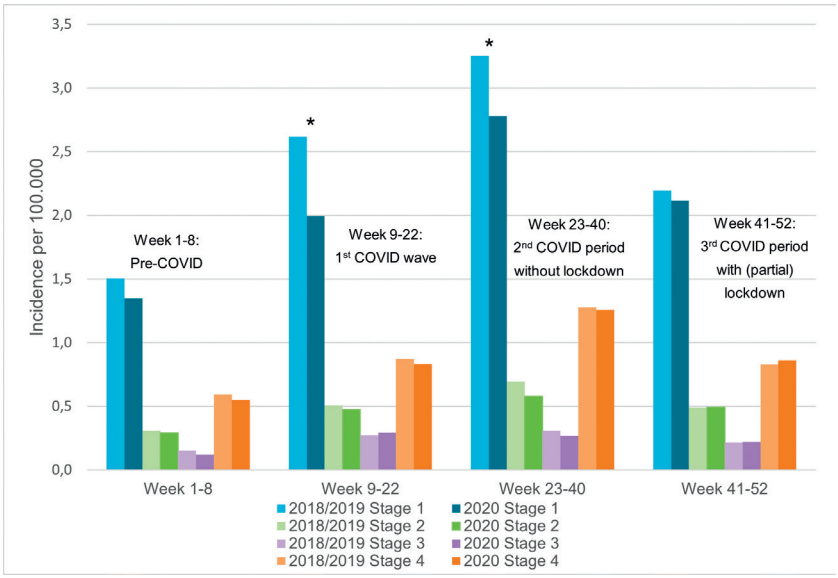
Supplementary material

a.



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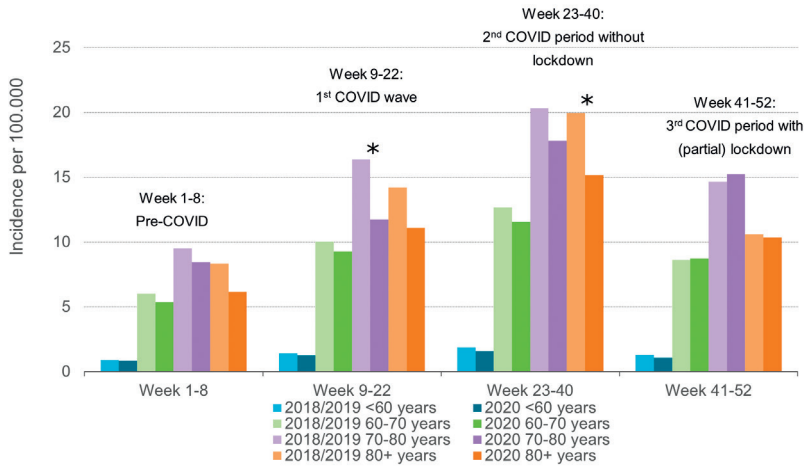
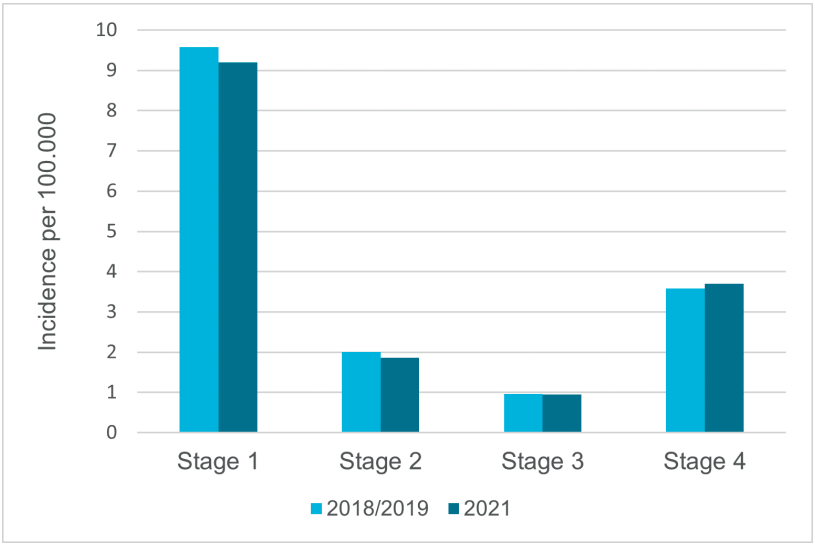


Figure 2. (a) Incidence of renal cancer per 100.000 person years per disease stage and (b) age at diagnosis, per time period in 2020 compared to the same time period in 2018/2019.

* The incidence is significantly lower ($p<0.01$) compared to the incidence of 2018/2019.

a.



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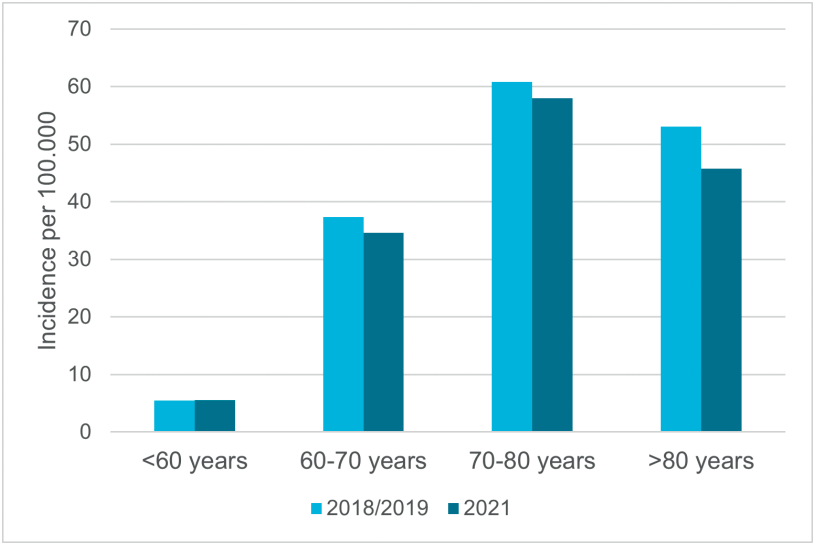

Figure 3. Incidence of renal cancer per 100.000 person years by (a) disease stage at diagnosis and (b) age at diagnosis in 2021 and 2018/2019.

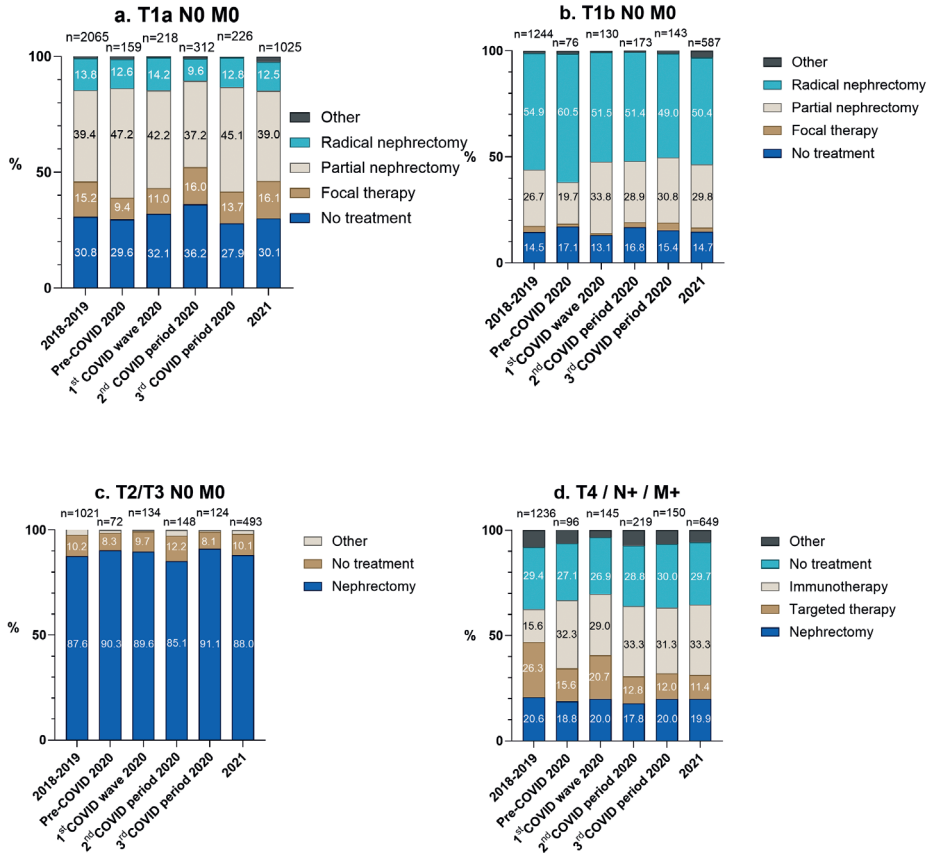

Figure 4. First-line treatment of patients diagnosed with renal cancer per disease stage and per period of diagnosis in 2020 and reference period 2018/2019.

COVID periods in 2020: Pre-COVID: week 1-8 2020, 1st COVID wave: week 9-22 2020, 2nd COVID period without lockdown: week 23-40 2020, 3rd COVID period with (partial) lockdown: week 41-52 2020

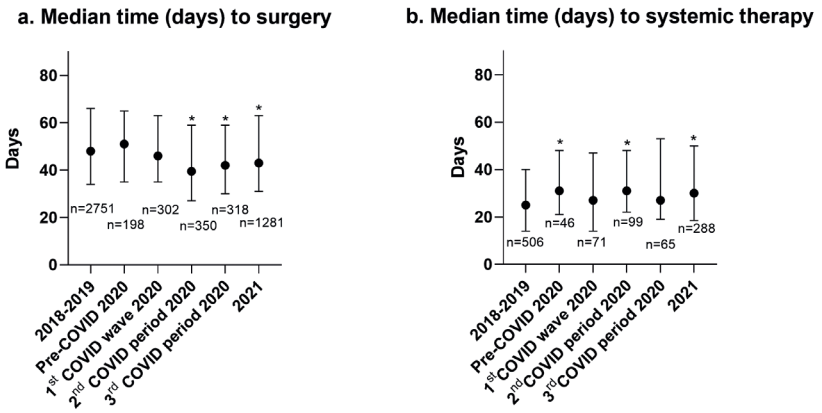

Figure 5. Median time with upper and lower quartile (in days) from diagnosis to (a) surgery (partial and radical nephrectomy) and (b) systemic therapy (immuno- and targeted therapy) per period in 2020 and in 2021 compared to the reference period 2018/2019.

* Time to treatment is significantly lower or higher ($p<0.05$), using the Mann-Whitney U test compared to 2018/2019.

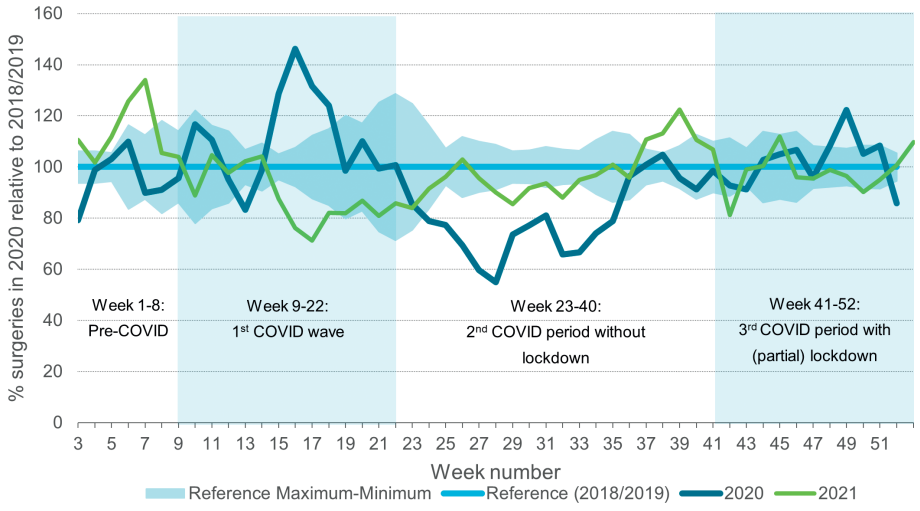

Figure 6. 3-week moving averages of number of (partial) nephrectomies in 2020 and 2021 relative to the reference period 2018/2019 (100%).

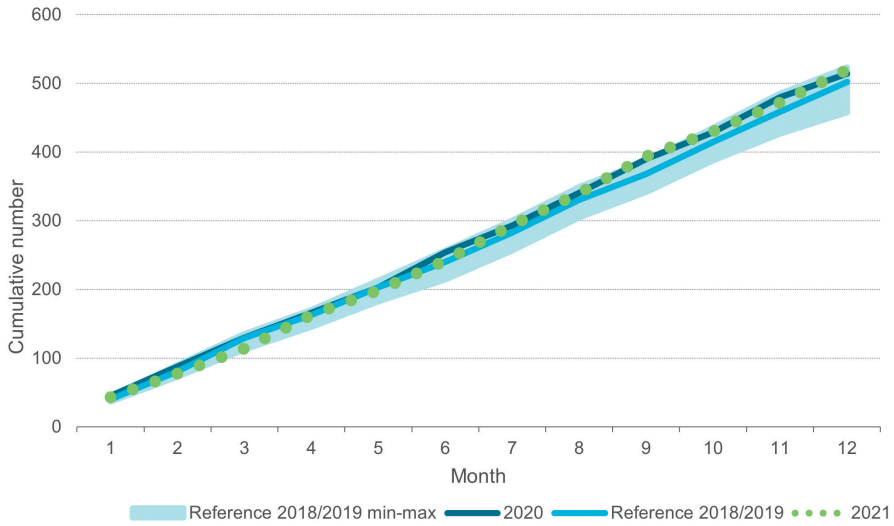

Figure 7. Cumulative number of patients newly diagnosed with metastatic renal cancer in 2020 and 2021 compared to the reference period 2018/2019.

Table 2. Logistic regression analyses with Odds Ratios (OR) of receiving treatment per disease stage and per period in 2020 and in 2021 compared to the reference period 2018/2019, adjusted for age at diagnosis.

	Reference 2018-2019	Pre-COVID Week 1-8 2020	1st COVID wave Week 9-22 2020	2nd COVID Period without lockdown Week 23-40 2020	3rd COVID period with (partial) lockdown Week 41-52 2020	2021
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
T1a N0 M0						
No treatment	ref	1.05 (0.71-1.57)	1.17 (0.83-1.64)	**1.36 (1.03-1.80)**	0.86 (0.61-1.20)	0.96 (0.80-1.16)
Focal therapy	ref	0.59 (0.34-1.01)	0.69 (0.45-1.08)	1.07 (0.77-1.48)	0.89 (0.60-1.33)	1.07 (0.88-1.32)
Partial nephrectomy	ref	1.33 (0.94-1.88)	1.09 (0.81-1.48)	0.92 (0.71-1.20)	1.30 (0.97-1.75)	0.98 (0.83-1.15)
Radical nephrectomy	ref	0.89 (0.55-1.44)	1.03 (0.69-1.54)	**0.67 (0.45-0.99)**	0.92 (0.61-1.39)	0.90 (0.72-1.12)
Other	ref	1.47 (0.34-6.39)	0.53 (0.07-3.98)	1.10 (0.32-3.76)	0.51 (0.07-3.81)	**2.61 (1.40-4.86)**
T1b N0 M0						
No treatment	ref	1.21 (0.56–2.24)	0.85 (0.47–1.54)	1.35 (0.83–2.19)	0.92 (0.53–1.58)	1.02 (0.75–1.40)
Focal therapy	ref	0.45 (0.06–3.31)	0.27 (0.04–1.98)	0.82 (0.29–2.32)	1.22 (0.47–3.17)	0.66 (0.33–1.31)
Partial Nephrectomy	ref	0.72 (0.40–1.29)	1.41 (0.95–2.09)	1.15 (0.80–1.64)	1.31 (0.89–1.93)	1.18 (0.95–1.48)
Radical nephrectomy	ref	1.31 (0.81–2.10)	0.87 (0.60–1.25)	0.88 (0.64–1.21)	0.81 (0.57–1.15)	0.84 (0.69–1.02)
Other	ref	1.23 (0.16–9.51)	0.74 (0.10–5.68)	0.55 (0.07–4.23)	1.31 (0.29–5.86)	**3.17 (1.55–6.46)**
T2/T3 N0 M0						
Nephrectomy	ref	1.49 (0.61–3.66)	1.29 (0.69–2.44)	0.88 (0.50–1.53)	1.44 (0.73–2.84)	1.07 (0.74–1.54)
No treatment	ref	0.63 (0.26–1.82)	0.92 (0.47–1.80)	1.11 (0.61–2.03)	0.84 (0.41–1.72)	0.98 (0.66–1.46)
Other	ref	0.62 (0.08–4.65)	0.32 (0.04–2.40)	1.17 (0.40–3.44)	0.34 (0.05–2.58)	0.81 (0.37–1.76)

Table 2. *(Continued)*

	Reference 2018-2019	Pre-COVID Week 1-8 2020	1st COVID wave Week 9-22 2020	2nd COVID Period without lockdown Week 23-40 2020	3rd COVID period with (partial) lockdown Week 41-52 2020	2021
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
T4 / N1 / M1						
Nephrectomy	ref	0.89 (0.52–1.52)	0.90 (0.58–1.40)	0.82 (0.56–1.20)	0.97 (0.63–1.49)	0.94 (0.74–1.20)
Targeted therapy	ref	**0.52 (0.29–0.91)**	0.70 (0.46–1.08)	**0.41 (0.27–0.62)**	**0.38 (0.23–0.63)**	**0.36 (0.27–0.47)**
Immunotherapy	ref	**2.73 (1.71–4.36)**	**2.14 (1.43–3.21)**	**2.84 (2.04–3.96)**	**2.62 (1.78–3.88)**	**2.84 (2.25–3.58)**
No treatment	ref	0.95 (0.57–1.59)	1.00 (0.65–1.55)	1.00 (0.70–1.42)	1.00 (0.70–1.60)	1.05 (0.83–1.33)
Other	ref	0.77 (0.33–1.82)	0.42 (0.17–1.06)	0.91 (0.52–1.58)	0.81 (0.41–1.59)	0.69 (0.47–1.02)

All statistically significant values are in **bold** (P<0.05).
Ref=reference, OR=odds ratio, 95%CI=95% confidence interval

Appendix A

Definitions

The NCR receives notifications of new cancer diagnoses from the automated nationwide network and registry of histo- and cytopathology (PALGA). In addition, renal cancers without pathological confirmation were retrieved by a linkage of the Dutch Hospital Data (DHD) to the NCR. Detailed data on patient characteristics (gender, age at diagnosis, postal code), tumor characteristics (morphology according to the international classification for Oncology (ICD-O) third edition and TNM disease stage according to the UICC Tumor-Node Metastasis classification1,2, and type (and date of start) of first-line treatment were available through the NCR.

Age at diagnosis was evaluated continuously and by category: <60, 60-70, 70-80 and >80 years.

All renal cancers (any grade) were categorised in four stage groups: 1) cT1a/N0-X/M0-X, 2) cT1b/N0-X/M0-X, 2) cT2-T3/N0-X/M0-X) and 4) cT4 and/or N+ and/or M+. Treatment was divided in 'no active treatment' (both including active surveillance and watchful waiting as it was not possible to differentiate between both based on the documentation in the medical files), partial nephrectomy, radical nephrectomy, focal therapy, targeted therapy, immunotherapy and other.

Statistical analyses

Descriptive statistics were used to give insight into patient- and tumor characteristics of patients diagnosed in 2020 (stratified by different time periods) and in 2021, versus patients diagnosed in the reference period 2018/2019.

The number of newly diagnosed renal cancers in 2020 and 2021 was calculated per week by using three-week moving averages and compared to 2018/2019 (averaged). Additionally, the relative change in the number of diagnoses was evaluated by considering the three-week moving average of 2018/2019 as 100%.

Incidence rates per 100.000 person years were calculated per predefined time period in 2020 and 2021 and compared to (the same period in) 2018/2019, stratified by disease stage and age, using the iri command in STATA.

For each disease stage, the distribution of different first-line treatments was described by time period in 2020 and 2021 versus the reference. Logistic regression analyses were performed to evaluate the age-adjusted probability of receiving a certain treatment in a time period in 2020 and 2021 compared to the reference period. Time from diagnosis to (partial) nephrectomy and systemic therapy (immunotherapy and/or targeted therapy) was calculated, stratified per time period in 2020 and 2021 and compared to the reference period using the Mann-Whitney U test.

To evaluate the effect of the COVID-19 outbreak on surgical volume, the three-week moving averages of the number of partial and radical nephrectomies in 2020 and 2021 were compared to the reference period by considering the reference period as 100%.

Finally, to provide some insight in whether a possible delay in diagnosis affected the disease stage at diagnosis, we assessed the cumulative number of patients diagnosed with metastatic disease per month in 2020 and 2021 and compared this with 2018/2019.

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6

Immunotherapy in Metastatic Renal Cell Carcinoma: Insights from a Dutch Nationwide Cohort

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Abstract

Targeted therapy with tyrosine-kinase inhibitors (TKIs) was the standard of care for metastatic renal cell carcinoma (mRCC) until recently, when new first-line combinations with immunotherapy (IO) were approved. This study evaluated the uptake of IO as both first-line and later-line treatments in routine clinical practice in the Netherlands.

Patients diagnosed with synchronous mRCC in 2018-2022 were identified from the population-based Netherlands Cancer Registry (n=2621). Median age was 70 years and 58% had clear-cell RCC. Overall, 55% received ≥1 line of systemic therapy, 7% underwent a cytoreductive nephrectomy (without systemic therapy) and the remaining 37% received best supportive care (BSC). Among systemically treated patients, the use of first-line TKIs decreased from 94% in 2018 to 21% in 2022, while the use of treatments including IO increased from 6% to 79%. Data from 2019-2020 showed that 32% and 10% of patients received any second-line and third-line therapy, respectively. Three-year overall survival of patients with synchronous mRCC increased over time from 20% (95%CI 16-23) in 2018 to 28% in 2021 (95%CI 24-33).

This analysis shows that approval of IOs since 2019 for mRCC have led to an immediate and large increase in use of IO to approximately 80% of systemically treated patients.

Introduction

In the Netherlands, 20% of renal cell carcinoma (RCC) patients present with metastases (synchronous mRCC) and 20-40% of patients with localised disease develop metastases during follow-up[1,2]. The mRCC treatment landscape has evolved from cytokines to tyrosine-kinase inhibitors (TKIs) to immunotherapy (IO)[3]. First-line IO combinations (IO-IO or IO-TKI) have shown superior efficacy over TKI monotherapy (sunitinib)[4,5]. Ipilimumab-nivolumab was the first approved combination in 2019, followed by pembrolizumab/axitinib (2020), cabozantinib/nivolumab (2022) and pembrolizumab/lenvatinib (2022)[3,6]. This study aimed to describe the uptake of IO as first- and later-line treatment in daily practice in the Netherlands, using a population-based cohort of synchronous mRCC patients. Also the trend over time in overall survival (OS) was described.

Methods

All patients diagnosed with synchronous mRCC between 2018 and 2022 were identified from the Netherlands Cancer Registry (NCR), maintained by the Netherlands Comprehensive Cancer Organisation[7]. Patient, tumor, and first-line treatment data were retrieved from the NCR for all patients. For patients diagnosed in 2019-2020, additional data on later treatment lines were collected within the PRO-RCC initiative (from diagnosis until 1 June 2022)[8]. Treatment was categorised as systemic therapy (+/- nephrectomy), nephrectomy only, and best supportive care (BSC). Systemic therapy was further divided into IO-IO, IO-TKI, TKI and IO monotherapy. OS was calculated using the Kaplan-Meier method, from date of diagnosis until death (event) or data cut-off at 31 January 2024 (censoring). For those alive (n=623), median follow-up until censoring was 31 months (IQR 21-45). All analyses were performed using SAS version 9.4. This study was approved by the NCR Privacy Review Board (24-00237).

Results

Between 2018 and 2022, 2621 patients were diagnosed with synchronous mRCC. Median age at diagnosis was 70 years (IQR 62-77), 68% were male and 58% had clear-cell RCC. The most common metastatic sites were lung (66%), bone (37%), and non-regional lymph nodes (34%). Additional descriptives are shown in Supplementary Table 1. Overall, 55% received systemic therapy, 7% underwent nephrectomy without systemic therapy, and the remaining 37% had BSC.

Treatment of mRCC has changed significantly over time. In 2018, 94% of systematically treated patients received first-line TKI (mainly pazopanib and sunitinib). From 2019 onwards, TKI use dropped to 21% in 2022, in favour of IO-IO combinations, increasing to 71% in 2022. IO monotherapy and IO-TKI were rarely used as first-line treatment (2-6%). Overall, 79% of systematically treated patients received IO (combination) therapy in 2022. Furthermore, a decreasing trend was observed in patients receiving systemic therapy (59% to 51%), whereas BSC (36% to 39%) and nephrectomy (6% to 10%) showed increasing trends (Figure 1, Supplementary Table 1).

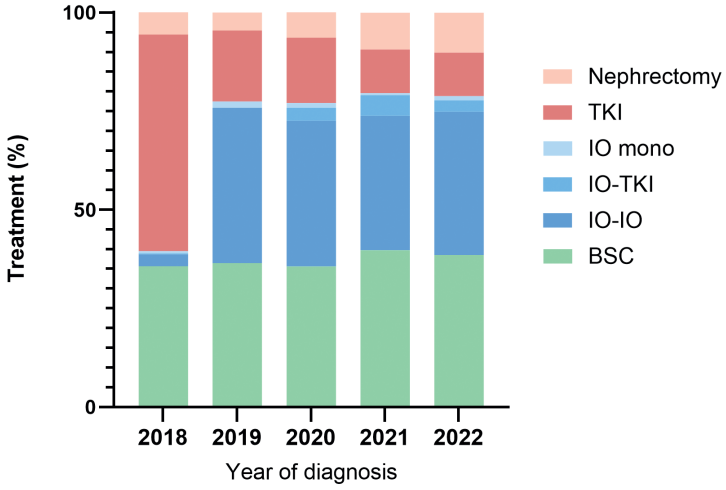

Figure 1. First-line treatment of patients with synchronous mRCC in 2018-2022 in the Netherlands

Abbreviations: mRCC; metastatic renal cell carcinoma, BSC; best supportive care, IO; immunotherapy, TKI; tyrosine kinase inhibitor, mono; monotherapy

Figure 2 shows treatment lines for patients diagnosed between 2019-2020. Data on treatment lines was collected from diagnosis until death for 64% of patients. For those alive at the end of follow-up (1 June 2022), median follow-up time from diagnosis was 26 months (IQR 22-32). After first-line IO-IO (n=388), 43% received maintenance IO and 18% second-line TKI. Slightly more than one-third (36%) with maintenance IO continued with second-line TKI. Among patients treated with first-line TKI (n=176), 22% received second-line IO, and 9% switched to second-line TKI. Overall, 32% and 10% of patients who received at least one line of systemic therapy (n=595) went on to second- and third-line therapy, respectively.

Three-year OS of mRCC patients increased from 20% (95%CI 16-23) in 2018 to 28% (95%CI 24-33) in 2021. Among patients receiving systemic therapy, three-year OS increased from 26% (95%CI 21-31) to 33% (95%CI 26-39) and for those receiving BSC from 5% (95%CI 1.8-8.2) to 14% (95%CI 9.4-19) (Figure 3).

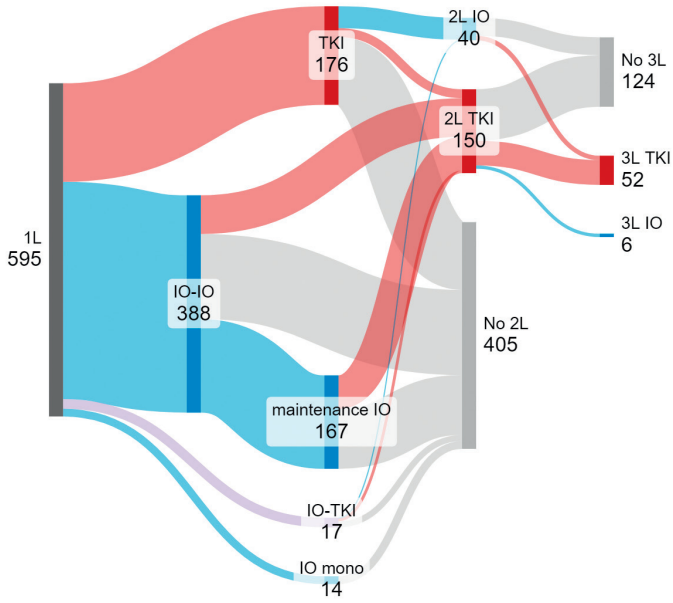

Figure 2. First- and later-line treatments in patients diagnosed in 2019-2020 with mRCC and treated with systemic therapy.

Abbreviations: 1L; First-line, 2L; Second-line, 3L; Third-line, IO; immunotherapy, TKI; Tyrosine Kinase Inhibitor

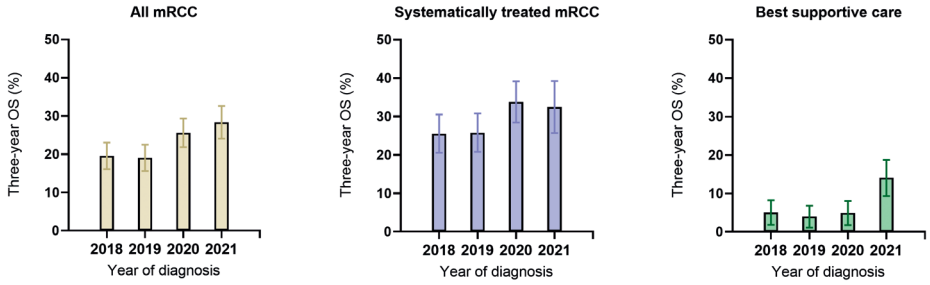

Figure 3. Three-year overall survival with 95%CI of patients diagnosed with mRCC in the period 2018-2021 by year (all mRCC/systemically treated mRCC/best supportive care)

Discussion

In summary, the treatment landscape for mRCC has shifted following the introduction of IO combination therapy. EAU guidelines recommend IO-based combinations (IO-IO or IO-TKI) for intermediate and poor risk IMDC with clear-cell mRCC, reserving TKI monotherapy for those who cannot tolerate IO or have specific non-clear-cell subtypes[5]. A clear increase in the use of first-line IO-IO was observed, while IO-TKI combinations were used in only a small minority of patients. The approval of cabozantinib/nivolumab and pembrolizumab/lenvatinib in 2022 could partly explain this. However, this difference may also reflect physician preference and experience, as pembrolizumab/axitinib was already approved in 2020[6].

Population-based data presenting the use of IO in unselected patients are scarce. In multicentre cohort studies from the UK[9] and the US[10], first-line IO combination therapy was used in 69% of patients in 2021 (UK) and 63% in 2018-2020 (US). Most patients in these studies, as in ours, did not receive any later-line treatment. This highlights the importance of selecting the optimal first-line treatment, as only a small proportion of patients will proceed to later-lines of treatment.

The introduction of new IO-based combinations has not led to an increase in patients eligible for systemic treatment, as the proportion receiving BSC slightly increased over time, while fewer patients received systematic therapy. However, for patients diagnosed in 2021-2022, treatment data was only available in the first year from diagnosis. Some of these patients may have received metastasis-directed therapy and active surveillance, which could explain the higher proportion of BSC in these years and the observed increased survival of patients receiving BSC.

We observed more favourable characteristics of patients treated with systemic therapy in recent years, particularly in patients receiving IO compared to those treated with TKI, but also in the BSC group (data not shown). This may be a result of the centralisation of systemic treatment for mRCC in the Netherlands, leading to a more selective use of systemic therapy, taking into account toxicity, quality of life and costs in addition to patient preference.

Strengths of our study include its unselected nationwide nature and detailed data on first and subsequent treatment lines. Limitations include lack of data

on metachronous mRCC and on later-lines of patients diagnosed after 2020. Follow-up data concerning patients in the 2019-2020 cohort was only complete for 64% on 1 June 2022. As 36% of patients were still alive at the end of follow-up, the use of later line treatments might be underestimated. Within the PRO-RCC initiative RCC patients will be prospectively followed until death and these data will allow analyses of both synchronous and metachronous mRCC patients in the near future[8].

Conclusion

The current analysis showed that the approval of IO as first-line treatment for mRCC in the Netherlands in 2019 led to an immediate and large increase in the use of IO for synchronous mRCC, with approximately 80% of systemically treated patients receiving IO in recent years. Survival of synchronous mRCC has improved in this time period. During the period covered by this study, the characteristics of patients receiving systemic treatment have evolved along with the introduction of IO. Other changes may also have had an effect. Therefore, the observed changes in OS cannot necessarily be contributed to the uptake of IO.

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Supplementary material

Supplementary Table 1. Characteristics of patients diagnosed with mRCC between 2018-2022, total and per year.

	All patients N=2621 (%)	**2018 N=501 (%)**	**2019 N=501 (%)**	**2020 N=517 (%)**	**2021 N=557 (%)**	**2022 N=545 (%)**
Gender, n (%)						
Male	1788 (68)	342 (68)	329 (66)	362 (70)	364 (65)	391 (72)
Female	833 (32)	159 (32)	172 (34)	155 (30)	193 (35)	154 (28)
Age at diagnosis						
Median (IQR)	70 (62-77)	70 (62-77)	70 (62-76)	70 (62-76)	71 (62-78)	69 (62-77)
Age at diagnosis, n (%)						
<60	506 (19)	98 (20)	102 (20)	97 (19)	110 (20)	99 (18)
61-70	754 (29)	137 (27)	137 (27)	161 (31)	144 (26)	175 (32)
71-80	899 (34)	166 (33)	179 (36)	181 (35)	195 (35)	178 (33)
81+	462 (18)	100 (20)	83 (17)	78 (15)	108 (19)	93 (17)
Histological confirmation, n (%)						
Yes	2148 (82)	395 (79)	422 (84)	432 (84)	452 (81)	447 (82)
No	473 (18)	106 (21)	79 (16)	85 (16)	105 (19)	98 (18)
Histology*, n (%)						
Clear-cell	1513 (58)	276 (55)	289 (58)	303 (58)	317 (57)	328 (60)
RCC NOS	348 (13)	56 (11)	82 (16)	71 (14)	81 (14)	58 (11)
Non-clear cell	760 (29)	169 (34)	130 (26	143 (28)	159 (29)	159 (29)
First-line treatment, n (%)						
Systemic therapy	1453 (55)	294 (59)	295 (59)	300 (58)	284 (51)	280 (51)
Nephrectomy	191 (7.3)	28 (5.6)	23 (4.6)	33 (6.4)	52 (9.3)	55 (10)
Best supportive care	977 (37)	179 (36)	183 (37)	184 (36)	221 (40)	210 (39)
Type of systemic therapy**, n (%)						
Ipilimumab/nivolumab	791 (54)	15 (5.1)	197 (67)	191 (64)	190 (67)	198 (71)
Pazopanib	272 (19)	147 (50)	43 (15)	40 (13)	28 (10)	14 (5.0)
Sunitinib	246 (17)	118 (40)	34 (11)	39 (13)	23 (8.1)	32 (11)
Cabozantinib	47 (3.2)	7 (2.4)	11 (3.7)	6 (2.0)	10 (3.5)	13 (4.6)
Pembrolizumab/axitinib	56 (3.9)	0 (0.0)	0 (0.0)	16 (5.3)	28 (10)	12 (4.3)
Other	41 (2.8)	7 (2.4)	10 (3.4)	8 (2.7)	5 (1.8)	11 (3.9)

Supplementary Table 1. *(Continued)*

	All patients N=2621 (%)	2018 N=501 (%)	2019 N=501 (%)	2020 N=517 (%)	2021 N=557 (%)	2022 N=545 (%)
Type of systemic therapy**, n (%)						
IO-IO	791 (54)	15 (5.1)	197 (67)	191 (64)	190 (67)	198 (71)
IO-TKI	63 (4.3)	1 (0.3)	0 (0.0)	17 (5.7)	29 (10)	16 (5.7)
TKI	573 (39)	275 (94)	90 (30)	86 (29)	62 (22)	60 (21)
IO mono	26 (1.8)	3 (1.0)	8 (2.7)	6 (2.0)	3 (1.1)	6 (2.1)
CRN**, n (%)						
Yes	237 (16)	76 (26)	61 (21)	57 (19)	24 (8.5)	19 (6.8)
Number of metastatic sites, n (%)						
0 - 2	1039 (40)	201 (40)	182 (36)	207 (40)	229 (41)	220 (40)
≥ 3	1582 (60)	300 (60)	319 (64)	310 (60)	328 (59)	325 (60)
Metastatic sites, n **(%)**						
Lung	1716 (66)	328 (66)	331 (66)	326 (63)	360 (65)	371 (68)
Liver	446 (17)	85 (17)	83 (17)	93 (18)	92 (17)	93 (17)
Adrenal	448 (17)	78 (16)	91 (18)	90 (17)	103 (19)	86 (16)
Bone	969 (37)	189 (38)	201 (40)	188 (36)	201 (36)	190 (35)
Lymph node	878 (34)	154 (31)	169 (34)	188 (36)	182 (33)	185 (34)
Brain	174 (6.6)	27 (5.4)	28 (5.6)	30 (5.8)	46 (8.3)	43 (7.9)
Other	631 (24)	120 (24)	119 (24)	124 (24)	139 (25)	129 (24)

* Only histologically confirmed renal cancers were included, ** Only systematically treated patients were included,

Abbreviations: SD; standard deviation, IO; immunotherapy, TKI; Tyrosine Kinase Inhibitor, mono; monotherapy, CRN; cytoreductive nephrectomy

7

Changes to Primary End Points in Randomised Clinical Trials on Immune Checkpoint Inhibitors in Urothelial, Renal Cell, and Lung Cancers: A Systematic Review

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Programmed cell death 1/programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) are important treatment options for many cancer types[1]. Urologic and lung cancers have early and multiple Food and Drug Administration (FDA) and European Medicines Agency–approved ICIs based on randomised clinical trials (RCTs)[2]. To weigh the strength of evidence, readers need complete and transparent information on design and methodology facilitated by mandatory RCT registration and adherence to CONSORT reporting guidelines[3]. We assessed how often primary end points in RCTs of ICIs were changed and the extent to which these changes were reported.

All phase-III RCTs assessing ICI in urothelial (UC), renal (RCC) and non-small cell lung cancer (NSCLC) published before October 10th, 2022 were identified through PubMed. Journal articles, supplementary files, and clinicaltrials.gov registrations were used to extract data on primary endpoint(s).

Three aspects of the primary endpoint were considered: the outcome measure (e.g., overall survival), the patient population in which it was assessed (e.g., biomarker-positive patients), and in case of >2 arms, specification of arms for primary comparison. This review was not preregistered. Full overview of all extracted data can be found at www.github.com/AnkeRichters. This study followed the PRISMA reporting guideline where applicable.

Thirty-eight RCTs involving 31.647 patients were identified (Table 1). Twenty-four RCTs (63%) changed at least 1 aspect of the primary end point (Table 2). Patient population and outcome measure changes occurred in 19 (50%) and 13 (34%) RCTs, respectively. Of 10 multigroup RCTs, 7 (70%) changed the specification of groups for comparison. Eight publications reported changing the primary end point, with 5 providing reasons for changes, mostly referring to other trials' results.

Changes to the primary endpoint during or after recruitment were omnipresent in RCTs with ICIs for patients with UC, RCC, and NSCLC. Most common were switching to or adding OS as an outcome measure and subpopulations based on PD-L1 expression. Ultimately, published data often do not allow readers to infer what the results would have been if the primary outcome had not been changed.

In some cases, these changes led to substantially altered conclusions. In CheckMate 9ER, the primary end point population was changed to also include

favourable-risk patients (capped at 25%) in addition to poor/intermediate-risk patients. By including this group in the primary end point population, nivolumab and cabozantinib now can be used in all risk groups instead of only poor/intermediate risk, although subgroup analyses showed no significant benefit for progression-free survival or OS for patients with favourable risk. Similarly, in Keynote 042, multiple nested PD-L1 subpopulations were added to the initial primary endpoint population. Although pembrolizumab showed no benefit among patients with tumours staining 1% to 49% for PD-L1, the addition of subpopulations with 1% or more and 20% or more led to FDA approval of pembrolizumab for all patients with PD-L1 staining of at least 1%.

These problems require greater transparency; editors should insist that changes to study design and outcomes are reported as stipulated by CONSORT. The International Committee of Medical Journal Editors requires enforcement of prospective registration of clinical trials, including the primary end points, to prevent selective reporting[4], but this appears to be left at the discretion of authors or peer reviewers. Mandatory supplementary publication of the initial and final trial protocol would allow readers to scrutinise end points themselves and should become more widely adopted. Poor reporting allows authors, intentionally or inadvertently, to escape scientific scrutiny of their trials. Missing or blacked out parts of supplementary protocols should not be acceptable.

JAMA, like many journals, instructs authors that "comparisons arrived at during the course of the analysis or after the study was completed should be identified as post hoc,"[5] but changes to primary outcomes remain prevalent[6] and may also extend to ICI RCTs in other cancer types. Sponsors, authors, peer reviewers, readers, regulators, and editors should work to improve transparency of these changes.

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Table 1. Overview of included randomised clinical trials on immune checkpoint inhibitors in urologic and lung cancer

RCT name	Tumor type	Arms	Number of patients	Original protocol available	Primary endpoint changed
CheckMate-017	NSCLC	Nivolumab vs. CT	272	Yes	Yes
CheckMate-026	NSCLC	Nivolumab vs. CT	514	No	Yes
CheckMate-057	NSCLC	Nivolumab vs. docetaxel	582	Yes	No
CheckMate-078	NSCLC	Nivolumab vs. docetaxel	504	No	No
CheckMate-227	NSCLC	PD-L1+: Nivolumab vs. nivolumab + ipilimumab vs. CT PD-L1–: Nivolumab + ipilimumab vs. nivolumab + CT vs. CT	1,739	Yes	Yes
CheckMate-816	NSCLC	Nivolumab + ipilimumab vs. nivolumab + CT vs. CT	505	Yes	Yes
CheckMate-9LA	NSCLC	Nivolumab + ipilimumab + CT	719	No	No
EMPOWER-Lung1	NSCLC	Cemiplimab vs. platinum-doublet CT	710	No	Yes
IMpower-010	NSCLC	Adjuvant CT + atezolizumab vs. adjuvant CT + BSC	1,005	No	Yes
IMpower-130	NSCLC	Atezolizumab + CT vs. CT	724	No	Yes
IMpower-150	NSCLC	Atezolizumab + CP vs. bevacizumab + CP vs. atezolizumab + bevacizumab + CP	1,202	Yes	Yes
IMpower-131	NSCLC	Atezolizumab + CP vs. atezolizumab + CnP vs. CnP	1,021	No	Yes
IMpower-132	NSCLC	Atezolizumab + PP vs. PP	578	No	Yes
Javelin-LUNG	NSCLC	Avelumab vs. docetaxel	792	No	Yes
Keynote-010	NSCLC	Pembrolizumab (2 mg/kg) vs. pembrolizumab (10 mg/kg) vs. docetaxel	1,034	No	Yes

Table 1. *(Continued)*

RCT name	Tumor type	Arms	Number of patients	Original protocol available	Primary endpoint changed
Keynote-024	NSCLC	Pembrolizumab vs. platinum-based CT	305	Yes	No
Keynote-042	NSCLC	Pembrolizumab vs. platinum-based CT	1,274	No	Yes
Keynote-189	NSCLC	Chemotherapy + pembrolizumab vs. CT + placebo	616	Yes	Yes
Keynote-407	NSCLC	Chemotherapy + pembrolizumab vs. CT + placebo	559	Yes	No
OAK	NSCLC	Atezolizumab vs. docetaxel	850	No	Yes
PACIFIC	NSCLC	Durvalumab vs. placebo	713	Yes	No
CLEAR	RCC	Lenvatinib + pembrolizumab vs. lenvatinib + everolimus vs. sunitinib	1,069	Yes	No
CheckMate-025	RCC	Nivolumab vs. everolimus	821	Yes	No
CheckMate-214	RCC	Nivolumab + ipilimumab vs. sunitinib	1,096	Yes	Yes
CheckMate-9ER	RCC	Nivolumab + cabozantinib vs. (nivolumab + ipilimumab) vs. sunitinib	651	Yes	Yes
IMmotion-010	RCC	Atezolizumab vs. placebo	778	No	No
IMmotion-151	RCC	Atezolizumab + bevacizumab vs. sunitinib	915	No	Yes
Javelin-renal-101	RCC	Avelumab vs. sunitinib	886	Yes	Yes
Keynote-426	RCC	Pembrolizumab + axitinib vs. sunitinib	861	Yes	No
Keynote-564	RCC	Pembrolizumab vs. placebo	1,406	Yes	No

Table 1. *(Continued)*

RCT name	Tumor type	Arms	Number of patients	Original protocol available	Primary endpoint changed
CheckMate-274	UC	Nivolumab vs. placebo	709	Yes	No
DANUBE	UC	Durvalumab + tremelimumab vs. durvalumab vs. CT	1,032	No	Yes
IMvigor-010	UC	Atezolizumab vs. observation	809	No	No
IMvigor-130	UC	Atezolizumab + CT vs. atezolizumab vs. CT + placebo	1,213	No	Yes
IMvigor-211	UC	Atezolizumab vs. CT	931	No	Yes
Javelin-bladder-100	UC	Avelumab + BSC vs. BSC	700	Yes	No
Keynote-045	UC	Pembrolizumab vs. CT	542	Yes	Yes
Keynote-361	UC	Pembrolizumab + CT vs. pembrolizumab vs. CT	1,010	No	Yes

Abbreviations: NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; UC = urothelial carcinoma; CT = chemotherapy; BSC = best supportive care; PP = platinum-based chemotherapy + pemetrexed.

Table 2. Primary endpoint information of randomised clinical trials where changes occurred

RCT name	Outcome changed	Population changed	Arms specification changed
CheckMate-017	ORR removed	-	N.a.
CheckMate-026	-	ITT changed to PD-L1+	N.a.
CheckMate-227	-	ITT changed to PD-L1+/TMB+	Compared arms changed for several outcomes
CheckMate-816	MPR changed to EFS and pCR	PD-L1+ changed to ITT	Arm A vs C changed to B vs C
EMPOWER-Lung1	OS added	ITT was removed	N.a.
IMpower-010	-	PD-L1+ subpop. added	N.a.
IMpower-130	OS added	tGE-WT subpop. added	N.a.
IMpower-150	OS added	PD-L1+ removed for 2 endpoints; tGE-WT added for 2 endpoints	No
IMpower-131	OS added	-	Arm A vs C changed to B vs C
IMpower-132	OS added	-	N.a.
Javelin-LUNG	-	PD-L1+ subpop. added	N.a.
Keynote-010	(Discontinuing) AE removed	PD-L1+ subpop. added	No
Keynote-042	-	Multiple PD-L1+ subpop. added	N.a.
Keynote-189	OS added	-	N.a.
OAK	-	PD-L1+ subpop. added	N.a.
CheckMate-214	ORR added	-	N.a.
CheckMate-9ER	-	Poor/int. risk changed to ITT	Arm B vs C was removed from endpoints

Table 2. *(Continued)*

RCT name	Outcome changed	Population changed	Arms specification changed
IMmotion-151	OS added	PD-L1+ subpop. added for 1 endpoint	N.a.
Javelin-renal-101	OS added	ITT changed to PD-L1+	N.a.
DANUBE	PFS changed to OS	ITT changed to PD-L1+ for 1 endpoint	Arm B vs C was added
IMvigor-130	-	PD-L1+ subpop. added for 1 endpoint	Arm B was added, but only tested for part of the outcomes
IMvigor-211	-	Multiple PD-L1 subpop. added to ITT	N.a.
Keynote-045	-	Multiple PD-L1 subpop. added to ITT	N.a.
Keynote-361	-	PD-L1 subpop. added to ITT	Compared arms changed for several outcomes

Abbreviations: n.a. = not applicable; ORR = objective response rate; ITT = intention-to-treat population; PD-L1 = programmed death-ligand 1; TMB = tumor mutational burden; MPR = major pathological response; EFS = event-free survival; pCR = pathological complete response; OS = overall survival; tGE-WT = T-effector tumor gene expression wildtype; AE = adverse events; PFS = progression-free survival.

8

The PRO-RCC Study: A Long-Term PROspective Renal Cell Carcinoma Cohort in the Netherlands, Providing an Infrastructure for 'Trial within Cohorts' Study Designs

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Abstract

Background

Ongoing research in the field of both localised, locally advanced and metastatic renal cell carcinoma has resulted in the availability of multiple treatment options. Hence, many questions are still unanswered and await further research. A nationwide collaborative registry allows to collect corresponding data. For this purpose, the Dutch PROspective Renal Cell Carcinoma cohort (PRO-RCC) has been founded, for the prospective collection of long-term clinical data, patient reported outcome measures (PROMs) and patient reported experience measures (PREMs).

Methods

PRO-RCC is designed as a multicentre cohort for all Dutch patients with renal cell carcinoma (RCC). Recruitment will start in the Netherlands in 2023. Importantly, participants may also consent to participation in a 'Trial within cohorts' studies (TwiCs). The TwiCs design provides a method to perform (randomised) interventional studies within the registry.

The clinical data collection is embedded in the Netherlands Cancer Registry (NCR). Next to the standardly available data on RCC, additional clinical data will be collected. PROMS entail Health-Related Quality of Life (HRQoL), symptom monitoring with optional ecological momentary assessment (EMA) of pain and fatigue, and optional return to work- and/or nutrition questionnaires. PREMS entail satisfaction with care. Both PROMS and PREMS are collected through the PROFILES registry and are accessible for the patient and the treating physician.

Trial registration

Ethical board approval has been obtained (2021_218) and the study has been registered at ClinicalTrials.gov (NCT05326620).

Discussion

PRO-RCC is a nationwide long-term cohort for the collection of real-world clinical data, PROMS and PREMS. By facilitating an infrastructure for the collection of prospective data on RCC, PRO-RCC will contribute to observational research in a real-world study population and prove effectiveness in daily clinical practice. The infrastructure of this cohort also enables that interventional studies can be conducted with the TwiCs design, without the disadvantages of classic RCTs such as slow patient accrual and risk of dropping out after randomisation.

Background

Worldwide, approximately 400 000 people are diagnosed with renal cell carcinoma (RCC) every year. This makes RCC the seventh most common form of neoplasm in the developed world, associated with more than 140 000 annual deaths[1]. In the Netherlands more than 2600 patients are diagnosed with RCC every year[2]. Over the past decades there is an increasing incidence of RCC in high-income countries, mostly due to the incidental detection of renal masses with abdominal imaging. As a result, renal masses are increasingly diagnosed at an early stage[3].

Treatment modalities for RCC have significantly developed over the last decades. However, many questions remain unanswered, such as the role of cytoreductive nephrectomy, the role of peri-operative treatment and the optimal sequence of systemic therapies[4]. Furthermore, the best strategy for follow-up should be evaluated.

For localised RCC, nephron-sparing (robot-assisted) partial nephrectomy has become common practice. In addition, ablative techniques and active surveillance for small renal masses (SRM) have entered daily practice[5,6]. Ablative techniques have shown to be a minimally invasive and safe treatment option for SRM in terms of complications, adverse events and early recurrence rates. However, oncological outcomes remain unclear[7], and it's long-term impact on health-related quality of life (HRQoL). Furthermore, active surveillance has proven to be a safe management for SRM, especially for older patients with comorbidities[8]. With several treatment options for localised RCC, more insight is warranted into finding the optimal care for the individual patient.

It is known that approximately one-third of the patients with RCC present with metastatic disease at diagnosis[1]. Immune therapy and targeted treatments have dramatically changed the treatment landscape for patients with metastatic RCC (mRCC)[9]. Interferon alpha and interleukin-2 were the mainstay of treatment and have been largely replaced in the last decades by vascular endothelial growth factor (VEGF) targeted therapies, mamalian target of rapamycin (mTOR) inhibitors and immune checkpoint inhibitors (ICI). Data from randomised controlled trials (RCTs) have shown higher response rates and improved clinical outcomes for these novel therapies[10-12].

Ideally, all new treatments should be compared to the standard of care in RCTs to determine efficacy. However, concurrent development of multiple new systemic therapies has resulted in a situation where most first line options have not been compared head-to-head. Also, data derived from RCTs are not completely generalisable to the real world practice, as it is known that a highly selected population is participating in clinical trials[9]. Only 5-15% of the patient population is participating in clinical trials, impeding representativeness[13,14]. As example, it is known that the median age of cancer trial participants is on average seven years younger compared to the general cancer patient population[15,16]. Thus, although data derived from RCTs can prove efficacy in a selective study population, such data do not prove effectiveness in daily clinical practice. Therefore, it is important to validate data from RCTs in observational research with real world data.

An alternative to classic RCTs are interventional studies with the Trial Within Cohorts (TwiCs) design, also known as 'cohort multiple randomised controlled trials' (cmRCT)[17,18]. Cohort participants will be selected based on their eligibility and randomised to a control or intervention arm at one moment in time. The TWiCs design eliminates some issues that are experienced in RCTs, such as slow patient accrual and risk of dropping out due to disappointment after randomisation.

In summary, the PROspective Renal Cell Carcinoma cohort (PRO-RCC) is an initiative to construct a nationwide long-term cohort of RCC patients in the Netherlands, enabling collection of long-term clinical data, patient reported outcome measures (PROMs) and patient reported experience measures (PREMs) to facilitate observational research and fill in remaining gaps in the field of RCC to improve HRQol and quality of care of all patients with RCC. Furthermore, interventional research can be conducted using the TwiCs design, which is embedded in the PRO-RCC infrastructure

Methods and Design

Inclusion of patients and informed consent

Our observational cohort is designed for continuous inclusion and longitudinal follow-up of newly diagnosed patients with RCC in the Netherlands (localised, locally advanced or with synchronous metastases) and also for patients with metachronous metastases. All Dutch inhabitants from the age of 18 years with histologically proven or high clinical suspicion of (m)RCC are eligible for

inclusion. Patients should be able to understand (written) Dutch language for participation. Written informed consent is mandatory for participation in the observational cohort. Study information is provided to each eligible patient by the treating physician or research nurse after initial diagnosis, but before the start of treatment during regular out-patient visits of the patient in the participating hospital. Patients will receive sufficient time to consider their participation.

Informed consent is given for the collection of PROMs, PREMs, (clinical) data sharing and data linking with the Netherlands Cancer Registry (NCR). Secondly, patients can opt in for potential participation in TwiCs. TwiCs can be conducted within the infrastructure of the cohort. Subjects who opt in for potential TwiCs participation, consent not to receive additional information if they are randomised to the control arm of a TwiCs study within the cohort. Only patients who are randomised for the interventional arm of a TwiCs will be informed about the study and receive additional study information. Before enrolment in the interventional arm additional informed consent for the specific TwiCs study is mandatory (Figure 1). Medical ethical approval of an institutional review board is required at initiation of each TwiCs, as is the case with any regular RCT. There is no limitation for participation of patients in randomised trials unrelated to PRO-RCC and patients can participate in different TwiCs at the same time, unless explicitly stated otherwise in a specific TwiCs protocol in which the patient is participating.

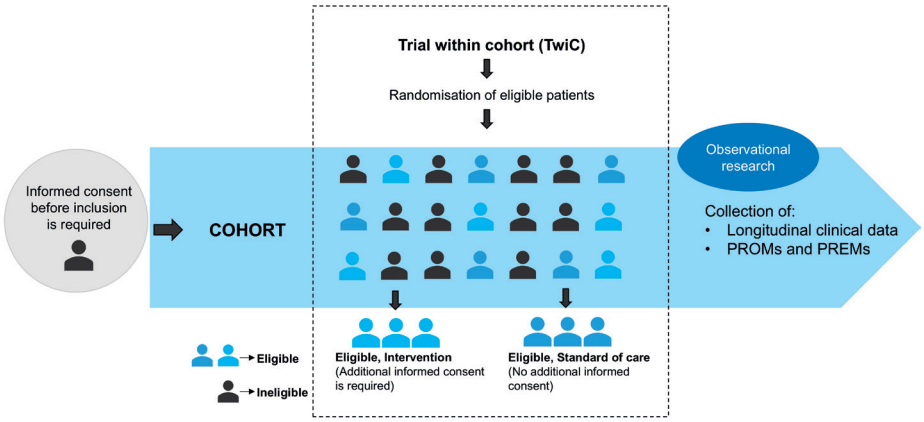

Figure 1. The 'trial within cohorts' design (TwiCs).

After ethical approval for an interventional TwiCs study, eligible patients are selected from the cohort. Only patients who have given informed consent for potential participation in a TwiCs upon entry in the PRO-RCC cohort are eligible for selection. After selection, eligible patients are randomised to the control or the intervention arm. Before inclusion in the intervention arm, separate informed consent has to be obtained from each patient. Patients in the control arm receive standard of care similar to the rest of the cohort and do not receive additional information. These patients have consented not to be notified of randomisation in a TwiCs control arm, as part of their consent to TwiCs participation upon entry in the PRO-RCC cohort.

Proceedings

Recruitment will start in the Netherlands in 2023. Nationwide expansion of participating hospitals is planned for subsequent years. Over 30 hospitals (community and academic) throughout the Netherlands have expressed their intention to participate in the PRO-RCC cohort. It is our aim to include approximately 70% of all newly diagnosed RCC cases in the Netherlands in PRO-RCC (approximately 1900 per year in case all hospitals in the Netherlands participate in PRO-RCC). No end date or recruitment target has been specified.

Before the start of prospective inclusion, a pilot study was performed. Extensive clinical data, largely according to the item list as defined for PRO-RCC, of approximately 150 patients were retrospectively collected from 2019 to 2020 for first evaluation. Based on the findings of this pilot, the final item list has been established. As the number of prospectively included patients in PRO-RCC will gradually increase over the years, we performed an additional data collection of all patients diagnosed with mRCC in 2018, 2019 and 2020 (N~1500). This data collection will provide the opportunity to study relevant research questions on a short term.

Clinical data collection

Clinical data collection is embedded in the NCR which is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL)[2]. The NCR has nationwide coverage since 1989. Well-trained data managers collect data of all patients diagnosed with cancer in the Netherlands. These data include patient- and tumor characteristics (comorbidities, morphology, RENAL score, PADUA score), disease stage (clinical and pathological TNM stage, WHO/ISUP grade) and treatment (type of surgery, surgical margins, type of systemic therapy). Vital status is recorded based on annual linkage with the Municipal Personal

Records Database which holds information on vital status and emigration of all Dutch inhabitants.

Additional PRO-RCC specific clinical items, such as laboratory tests, complications/toxicity, and specific details consisting systemic therapy, are collected from the medical files by the data managers.

In case of localised RCC, the following laboratory results are recorded: hemoglobin, creatinine and eGFR at diagnosis and at 6 months after local treatment. In case of mRCC hemoglobin, creatinine, eGFR, thrombocytes, neutrophils, calcium, albumin and LDH measurements are retrieved from the medical file at diagnosis, and before the start of each line of a systemic treatment.

Furthermore, 30 day-complications and the Clavien Dindo grade are registered for local treatments. The additional collection of items on systemic treatment consists of specific details concerning systemic therapy (e.g. dose, number of cycles, modifications, complications/toxicity, use of immunosuppressive drugs), clinical response to the systemic therapy and unexpected emergency room visits and/or hospital admission.

Clinical data collection will start for all patients 7 months after diagnosis. Thereafter, for patients with mRCC additional data will be collected one year after the first registration at 7 months, and a last time shortly after the patients has been deceased. For localised RCC the exact data collections time points have yet to be determined.

Collection of PROMs and PREMs

Patients participating in PRO-RCC will receive online PROMs and PREMs questionnaires. These questionnaires are collected with the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry[19], which can be linked to the clinical data of the NCR. Information on comorbidity, marital status, educational level, and employment status will be registered in the baseline questionnaire. Furthermore, questionnaires on HRQoL, using the Dutch validated EORTC Quality of Life Questionnaire (QLQ-C30)[20] and Dutch version of the EuroQOL groups health status measure EQ-5D-5L[21], will be collected at diagnosis, 15 weeks, 6 months, one year, and thereafter yearly until five years of follow-up or death (Figure 2).

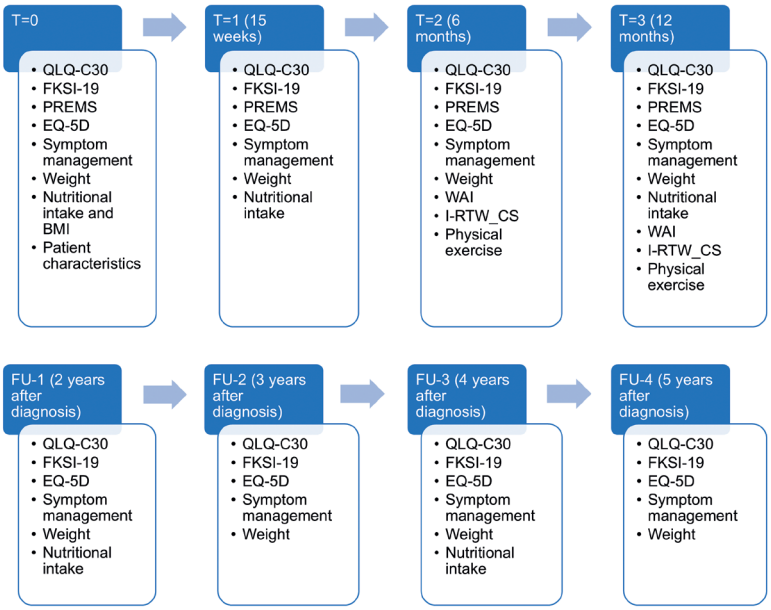

Figure 2. Overview of the collected patient reported outcome- and experience measures over time.

T=Time, FU=Follow-up

Symptom monitoring

Patient-reported symptoms will be collected online through the newly developed 'SYMPRO 2.0' application (mobile website), which is incorporated in PROFILES[19,22]. The SYMPRO 2.0 approach is described in detail elsewhere[23]. SYMPRO 2.0 allows the patient, treating physician and nurse to monitor symptoms. In the first year following diagnosis patients are requested to fill in a RCC specific symptom list, monthly in the first year, or more frequently if so desired by the participant with a maximum of once daily. The RCC specific symptom list will be collected yearly up to five years after the first year (Figure 2). If patients receive any systemic therapy, then a treatment-specific symptom list, instead of the RCC specific symptom list, will be collected weekly up to one year. This symptom list is retrieved from the side-effects application 'BijwerkingenBijKanker.nl'[24].

All symptoms are based on the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE)[25]. If necessary items were not available in the PRO-CTCAE, they were formulated in the PRO-CTCAE code by researchers and health care professionals and tested by health care professionals and laymen. The RCC-specific symptoms are based on the

National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy – Kidney Symptom Index 19 (FKSI-19)[26] and recoded into PRO-CTCAE items.

After each assessment by the patient, an overview of symptoms over time is available, which is also accessible online for the treating physicians and oncology nurses. Furthermore, alerts are forwarded to the patient if a selected symptom exceeds a particular threshold (such as the combination of diarrhea and vomiting for more than one day) or according to the composite grading algorithm that has been developed for the PRO-CTCAE[25]. If preferred in a participating hospital, alerts can also be forwarded by e-mail to the oncology nurse. Importantly, patients are instructed not to rely on this email system and to contact their physician in case of an alert and to follow the regular instructions provided at the treatment initiation.

Collection of additional questionnaires regarding nutrition, fatigue and pain and return to work

Optionally, questionnaires of nutritional intake, fatigue, pain and return-to-work are assessed if the subject has consented to these in the PROFILES application. Nutrition will be monitored by registering all foods and drinks during two weekdays and one weekend day, using the 'Eetmeter' from the Netherlands Nutrition Centre [Dutch: Voedingscentrum][27]. After registration, results of the 'Eetmeter' are shared in the secure PROFILES environment. It is requested to fill in the intake at diagnosis, after 15 weeks, and after one and three years (Figure 2). On these moments waist and hip circumference will be measured using a flexible measuring tape that is provided to the patient. The waist circumference and waist-to-hip ratio gives a global indication of the intra-abdominal fat mass[28]. Decreased intake and cachexia can occur during systemic treatment of mRCC, in particular with targeted therapies. In order to interpret the results with a more complete overview of the lifestyle, the 'SQUASH' questionnaire on physical exercise is added[29].

If moderate or severe fatigue or pain has repeatedly been reported in the SYMPRO 2.0 app for a period of two weeks, then optionally patients can keep record of a detailed fatigue or pain diary using Ecological Momentary Assessment (EMA) with the Ethica application[30,31]. The results of the questionnaires will be summarised in a report, that can be shared with the treating physician or nurse. Based on these data it will be possible to evaluate whether early detection

of these symptoms can prevent further deterioration and maybe long-term complaints.

Questionnaires on return-to-work are optional if (1) there is an employment contract at diagnosis, and (2) if own or adjusted work activities have been performed in the 4 weeks preceding the diagnosis. If both requirements are met, patient can opt in for questionnaires on work at 6 months and 1 year after diagnosis. It is known that the impact of cancer on work can be significant[32]. The 'Work Ability Index' (WAI) and the 'Successful Return-To-Work Questionnaire for Cancer Survivors' (I-RTW_CS) will be used[32,33].

PREMS

PREMs will be collected at diagnosis, 15 weeks, 6 months and one year, consisting of several questions regarding satisfaction with care. This questionnaire has been developed by the Dutch Federation of Cancer Patient Organisations [Dutch: Nederlandse Federatie van Kankerpatienten organisaties] (NFK)[34] in collaboration with the Dutch patient association for bladder or kidney cancer [Dutch: Leven met blaas- of nierkanker][35].

Governance

PRO-RCC is registered as foundation and is governed by committees consisting of medical oncologists, urologists and epidemiologists. A separate scientific advisory committee reviews new research proposals based on scientific value.

Patient and public involvement

The Dutch patient association for bladder or kidney cancer (Dutch: Leven met Blaas- of Nierkanker) were consulted in setup of the study. They will continue on providing input on scientific priorities, as they are a part of the PRO-RCC scientific advisory committee. Furthermore, they facilitate communication of study findings to patients.

Safety

Participants can withdraw from the project or related studies at any time and for any reason without any consequences. The non-interventional nature of this registry precludes the occurrence of adverse events as a result of participation. However, as mentioned above, there will be monitoring of symptoms from received treatments during this study through PROFILES. This will not be used as replacement for instructions from the treating physician and nurse. The symptom monitoring can be used as add-on in the outpatient clinic. Patients

will receive instructions concerning how and when to contact their treating physician with any alert. Furthermore, data on symptoms and medication agent(s) will be shared with pharmacovigilance centre Lareb[36]. Lareb will monitor the data for outliers and discrepancies in prevalence of symptoms compared to the summaries of product characteristics of the particular agents.

Discussion

The aim of PRO-RCC is to construct a nationwide cohort for patients with (m)RCC to collect real-world clinical data, PROMs and PREMs to facilitate observational research and provide a platform for interventional studies with the TwiCs design. Furthermore, PRO-RCC encourages data sharing and collaborations with external groups. Similar initiatives in the Netherlands have already proven its efficacy in the Dutch 'Prospective Bladder Cancer Infrastructure' (ProBCI)[37,38] and in the Dutch 'Prospective Nationwide Colorectal cancer Cohort' (PLCRC)[39,40].

PRO-RCC aims to achieve high recruitment rates within the cohort, allowing to conduct sufficient data analyses and providing an infrastructure for interventional studies. Such interventional studies can be conducted within PRO-RCC using the TwiCs design. The main advantage of TwiCs is improved recruitment rates, as eligible patients can be selected from the cohort database. Additional informed consent is only necessary from patients randomised for intervention. Therefore, the TwiCs design eliminates the barrier for patients to consent to randomisation with the risk of not being offered the preferred treatment[41]. Furthermore, the database provides an adequate representative sample of the control group with less selectiveness, as these patients cannot withdraw due to e.g. disappointment. The approach enables more direct and indirect comparisons, as all treatments have the same "treatment as usual" comparator and use the same core outcomes. The TwiCs design is only suited for interventional trials that compare the experimental arm to 'standard of care' and for research questions with outcomes that are easily measured and collected within the entire cohort. Also, the feasibility of conducting a TwiCs study hinges on the ability to identify eligible patients for the study in the cohort. Consequently, if the inclusion criteria cannot be established within the cohort, the execution of a TwiCs study becomes unfeasible. For instance, the identification and selection of patients with synchronous metastatic RCC and/or metachronous metastatic RCC are achievable within the cohort.

Furthermore, the treatment that is offered should have high acceptability. It should be noted that not all research questions can be addressed in a TwiCs design, such as closed trial designs with masking or a placebo arm. In addition, TwiCs with treatments not desired by patients are less suitable as there could be difficulties with recruitment in the interventional arm[17].

The clinical data collection of all patients diagnosed with mRCC in the period 2018-2020 through the NCR will enable analyses in a real world setting in short time. Starting in 2023 clinical data of newly diagnosed patients will be collected. These real-world clinical data will contribute to the knowledge of effectiveness of treatments in daily clinical practice. Furthermore, the cohort will enable subgroup analyses, as specific treatments are not always analysed in subgroups, such as in non-clear-cell RCC or in older patients, as both groups are underrepresented in clinical trials. In addition, the cohort will provide sufficient data on HRQOL and health care costs of different (novel) treatments, which are important considerations in (shared) decision making.

Conclusion

Altogether, the PRO-RCC cohort will provide a nationwide infrastructure for observational and interventional research, contributing to the evidence of clinical practice and creating opportunities for improvement of quality of care and quality of life of patients with RCC.

Declarations

Ethics approval and consent to participate

This multicentre study received approval by the medical ethical review board of the Amsterdam University Medical Center, The Netherlands in 2022 (2021_218). All TwiCs to be conducted within this infrastructure will require separate approval from a medical ethical review committee / institutional review board. All methods will be conducted in accordance with the ethical standards of the declaration of Helsinki and will be in accordance with relevant guidelines and regulations. Informed consent will be obtained from all patients before inclusion.

Dissemination policy

All scientific output and developments concerning PRO-RCC will be publicly available through the project website (www.pro-rcc.nl). The Dutch PRO-RCC

newsletter is open for registration to all patients, clinicians, and researchers who express interest in subscribing.

List of abbreviations

EMA: Ecological Momentary Assessment
HRQo: Health-Related Quality of Life
IKNL: Netherlands Comprehensive Cancer Organisation
mRCC: Metastatic Renal Cell Carcinoma
NCR: Netherlands Cancer Registry
NFK: Dutch Federation of Cancer Patient Organisations
PRO-RCC: PROspective Renal Cell Carcinoma cohort
PROMs: Patient Reported Outcome Measures
PREMs: Patient Reported Experience Measures
PRO-CTCAE: the common terminology criteria for adverse events.
PRO-BCI: Prospective Bladder Cancer Infrastructure
PLCRC: Prospective Nationwide Colorectal cancer Cohort
PROFILES: Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship
RCC: Renal Cell Carcinoma
RCTs: Randomised Controlled Trials
SRM: Small Renal Masses
TwiCs: Trial within Cohorts

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9

General Discussion and Future Perspectives

This thesis evaluates various aspects of kidney cancer care through the analysis of real-world data. It offers valuable insights into current clinical practices and oncological outcomes, which can be used to guide and enhance future clinical practice. The findings demonstrate notable progress in the field, while also revealing critical gaps and areas that require further investigation. This general discussion reflects on the key insights of the studies presented in the previous chapters. Future perspectives and opportunities are discussed as well.

Consider biological age instead of calendar age; a shift in patient assessment

The findings described in **Chapter 2** reveal differences in the management and outcomes of elderly diagnosed with renal cell carcinoma (RCC) compared to their younger counterparts. In more recent years, elderly patients –particularly those aged 80 years and above– are less frequently treated with active therapy, regardless of tumour stage. Among octogenarians no survival improvement is observed in the metastatic setting. In contrast, younger patients experience more favourable trends in survival outcomes.

As life expectancy continues to increase, it becomes ever more important that treatment decisions are guided by comprehensive evaluations of comorbidity, frailty, and patient preferences, rather than calendar age alone. Such an approach can help ensure that older patients who are likely to benefit from active treatment are not denied access to potentially life-prolonging therapies. This could be achieved by taking a structured approach to the management of elderly patients and by incorporating tools such as the geriatric frailty scale[1,2]. Further research is needed to optimise systemic treatment strategies for elderly patients who are likely to benefit. Such research should consider the physiological changes associated with ageing that may affect both the treatment effectiveness and how well it is tolerated[3].

Furthermore, quality of life and functional independence are important outcomes for elderly patients. Therefore, treatment decisions should be guided not only by the goal of prolonging life expectancy, but also by the impact of treatment on daily functioning and overall well-being. Patient-reported outcome measures (PROMs) can provide valuable insights into the impact of a certain treatment in older patients and can be used to further develop shared decision-making approaches tailored to elderly. Additionally, the growing multicultural nature of Dutch society introduces complexity to shared decision-

making, as cultural differences in beliefs, values and communication styles may influence patient and family preferences. It is therefore essential to recognise and integrate these cultural factors into the decision-making process.

Minimum volume standards are necessary to ensure high-quality kidney cancer care, but should not compromise accessibility

Chapter 3 examines variation in the management of cT1 RCC in the Netherlands over time, with a focus on adherence to the Dutch surgical volume standards for hospitals performing RCC surgery. High-volume centres appear to be more consistent in adhering to the guidelines, particularly with regard to the preferred use of partial nephrectomy over radical nephrectomy in cT1 RCC[4]. Another key finding is the unequal access to focal therapy among patients with cT1a RCC. Geographic differences in the proportion of patients treated with focal therapy are found based on patients' postal codes. It is crucial that all patients have equal access to high-quality healthcare. A shared decision-making approach should be adopted, in which all treatment options are discussed transparently and carefully considered, regardless of the hospital where a patient is diagnosed or the treatments available.

According to the current Dutch volume standards, hospitals should perform a minimum of 20 radical nephrectomies per year, with the same threshold applied to partial nephrectomies[5]. These thresholds are intended to increase surgical expertise and improve peri-operative outcomes. A recent systematic review by the EAU Guidelines Panel confirmed that higher hospital volumes are associated with better perioperative outcomes, including lower complication rates, shorter hospital stays, fewer positive surgical margins, and reduced need for transfusions[6]. Although perioperative outcomes are important, it could be misleading to focus solely on these measures given that the main goal of surgery is the long-term oncological outcome. The publication of the *Integraal Zorgakkoord (IZA)* in 2022[7] introduces additional complexity in the centralisation of cancer care – both in general and specifically in renal cancer. Hospitals are required to perform at least 50 active treatments annually for localised RCC including partial nephrectomy, radical nephrectomy or focal therapy; notably active surveillance is excluded. Such volume thresholds may introduce unintended incentives. Urologists could feel compelled to prioritise surgical treatment in order to meet volume requirements, even when less invasive options, such as focal therapy or active surveillance, might be more

appropriate. This risk could undermine the principle of shared decision-making, where treatment choices should be guided by clinical suitability and patient preferences. Next to the requirement concerning localised RCC, IZA also stated that hospitals that provide treatment for metastatic RCC must have a minimum annual volume of 50 patients treated with systemic therapies, including at least 10 new patients. The centralisation of systemic therapy may enhance expertise and improve the quality of care, as knowledge and experience with complex (immuno)therapies are concentrated within high-volume centres in a rapidly evolving therapeutic landscape.

While centralisation has been associated with improved peri-operative outcomes and enhanced expertise, it may simultaneously reduce accessibility, which highlights the importance of maintaining a careful balance. A recent nationwide 'flashmob study' in the Netherlands showes that, many cancer patients are willing to travel for better care, especially to hospitals with more experience of their specific type of cancer. However, this willingness varied across different groups of patients. Higher levels of willingness to travel are found among highly educated patients, those with rare cancers and those with better physical functioning. Conversely, the burden of travel remains a concern, particularly for older patients or those with limited physical capacity[8]. Additionally, the type of treatment could influence patients' willingness to travel. For example, patients may be more willing to travel for a one-time procedure, rather than for treatments requiring multiple hospital visits.

In the near future, it would be interesting to analyse the impact of centralisation in the Netherlands. Such an evaluation could provide valuable insights into how concentration of care affects treatment quality, outcomes, and accessibility. Comparative analyses with other countries, such as the United Kingdom - where major system changes in cancer care have demonstrated both benefits and challenges[9]- may help to identify best practices and guide future policy development.

Upfront cytoreductive nephrectomy should be considered in selected patients with metastatic RCC in the immunotherapy era

Chapter 4 addresses the ongoing debate concerning the role of cytoreductive nephrectomy (CN) in the immunotherapy era. As systemic treatments continue to evolve, the timing and value of CN remains a subjects of discussion. Although

prospective randomised data are still awaited, real-world evidence can offer valuable insights to guide current clinical practice.

From the nationwide cohort study performed, it is concluded that upfront CN is associated with improved overall survival in patients with metastatic RCC treated with immunotherapy (IO), while this association is not observed in patients treated with Tyrosine Kinase Inhibitors (TKI). Patients receiving upfront CN generally have a lower disease burden, with fewer metastatic sites, lower rates of T4 and/or N1 staging, better performance status, and are more frequently classified as IMDC intermediate rather than poor risk. Although statistical adjustments are made to account for baseline differences between patients with and without upfront CN, the risk of residual confounding cannot be excluded.

These findings support the strategy of performing upfront CN in patients with low-volume disease and favourable prognostic factors, particularly those who do not yet require systemic therapy at the time of diagnosis[10]. In such patients, upfront CN may delay tumour progression and disease progression[11], and, as suggested by our study, potentially improve survival.

Despite these observations, several important questions remain unanswered, particularly regarding the optimal timing of CN. Nevertheless, conducting randomised trials in this setting is known to be challenging. For example, SURTIME suffered from slow accrual and substantial crossover between treatment arms, limiting interpretability[12]. Current randomised studies primarily focus on deferred CN following immunotherapy. Based on our findings, future research should also explore the potential role of upfront CN in the immunotherapy era, particularly in well-selected patients who do not yet require immediate systemic treatment.

For patients that are not suitable for surgery, alternative cytoreductive strategies could also be considered. Emerging local treatment modalities such as stereotactic body radiation therapy (SBRT) may offer a less invasive option[13]. Early studies in oligometastatic RCC suggest that SBRT can provide local control or metastasis-directed therapy, potentially delaying the initiation or modification of systemic treatment without compromising oncological outcomes[14-16]. Although long-term data remain limited, SBRT represents a promising complement to cytoreductive treatment in selected patients and warrants further evaluation in future clinical trials.

Implement necessary changes to clinical practice as rapidly as during the COVID-19 pandemic

Chapter 5 evaluates the impact of the COVID-19 pandemic on RCC care in the Netherlands, focusing on changes in diagnoses and treatment patterns. During the first COVID-19 wave, a decrease in new RCC diagnoses is observed, particularly in cT1a/T1b RCC. Treatment modifications are limited and largely in line with adapted guidelines, with fewer surgeries for cT1a RCC in favour of active surveillance and a preference for targeted therapy over immunotherapy in the metastatic disease. No increase in advanced-stage RCC is observed until the end of 2021. These findings suggest that short-term delays in the management of localised RCC, especially small renal masses, may be clinically safe, supporting current trends toward active surveillance in selected patients[17,18].

Beyond these trends, the pandemic highlights the adaptability and resilience of the Dutch healthcare system. Despite significant challenges, RCC care largely continued according to adapted guidelines, demonstrating that essential oncological care can be maintained even under unprecedented circumstances. This observation aligns with reports from other cancer types during the same period[19].

Finally, the COVID-19 experience provides lessons for future clinical practice. While changes in routine care often take considerable time[20], the pandemic showed that rapid implementation of new guidelines is possible when there is a widely shared sense of urgency. In order to keep improving healthcare, we should implement necessary changes to clinical practice with the same sense of urgency. Furthermore, future research should also investigate whether incidence rates increased after 2021, and more specifically, whether a stage shift occurred due to missed diagnoses, as such delays could have significant implications for patient outcomes and survival[21].

Direct head-to-head comparisons between IO-IO and IO-TKI regimens as first-line therapy are warranted

In **Chapter 6**, we evaluate the use of immunotherapies (IO-IO, IO-TKI, and IO monotherapy) for metastatic RCC in routine clinical practice in the Netherlands, including both first- and subsequent-line treatments, using nationwide data. There are several important findings.

Following the introduction of immunotherapies as first-line treatment in 2019[22], its use increases rapidly, from 6% to 79% in 2022, while the use of first-line TKI decreases from 94% to 21%. Of those receiving first-line systemic therapy, 32% and 10% receive second-line and third-line treatment, respectively. Three-year overall survival for patients with synchronous metastatic RCC improves significantly, from 20% in 2018 to 28% in 2021. For patients receiving systemic therapy, the overall survival improves from 26% to 33%. Over time, patients receiving systemic treatment increasingly present with more favourable baseline characteristics. We hypothesise that the observed improvements in overall survival are likely to be attributable not only to the introduction of new therapies, but also to more refined patient selection. These trends may partly reflect the centralisation of systemic treatment in the Netherlands, suggesting enhancement of clinical expertise in patient selection and monitoring.

The use of IO based combinations (either IO-IO or IO-TKI) in the first-line for patients with intermediate- or poor-risk clear-cell metastatic RCC aligns with the recommendations of the EAU guidelines[4]. We observe a clear preference for IO-IO combinations, as IO-TKI combinations are used for only a minority of patients (2-6%). This may reflect clinicians' preference to ensure that eligible patients receive ipilimumab-nivolumab, which is approved exclusively as first-line treatment for intermediate- or poor-risk clear-cell metastatic RCC. While both IO-IO and IO-TKI are recommended by the EAU guidelines, direct head-to-head comparisons are lacking. A recent meta-analysis indicated that IO-TKI may be more beneficial than IO-IO as a first-line treatment, but the results should be interpreted with caution due to the heterogeneity of the trials[23]. It is crucial to select the most effective first-line treatment, given that only 32% and 10% of patients in our cohort subsequently receive second- and third-line therapy, respectively. Well-designed randomised trials and high-quality observational real-world data are therefore needed to determine the optimal first-line strategy. Registries such as the PROspective Renal Cell Carcinoma (PRO-RCC) cohort can provide valuable insights into the effectiveness and safety of emerging systemic therapies in routine clinical practice, complementing evidence from clinical trials and supporting clinical decision-making.

More transparency is needed regarding modifications of primary endpoints in oncology clinical trials

In **Chapter 7**, we demonstrate that in 24 of 38 (nearly two-thirds) of randomised trials investigating immunotherapy for bladder, lung, and kidney cancer,

adjustments are made to the primary endpoints. These modifications include changes to the study population, outcomes, and comparisons between groups. The most frequent adjustments involve adding overall survival as an outcome measure and conducting additional analyses in biomarker-positive subgroups. Contrary to current guidelines, only 8 of the 24 studies report these changes transparently. The lack of transparency regarding such modifications compromise the interpretability of trial results and undermines their scientific reliability.

A study by Florez et al. similarly assesses the frequency of primary endpoint changes in clinical oncology trials and investigates whether these changes are associated with trial positivity. Of the 755 included trials, 19% have primary endpoint changes, and 70% does not disclose these changes within the manuscript. Multivariable analysis demonstrates that primary endpoint changes are associated with trial positivity[24].

Despite efforts to establish trial registration regulations[25,26], the lack of clarity among randomised trials remains a matter of concern. Greater transparency regarding protocol modifications –including the context and rationale for changes made after trial initiation– is essential for accurate interpretation and validation of trial results. To achieve this, stricter measures should be implemented, such as the mandatory publication of both initial and final trial protocols, with clear documentation of any amendments within the published manuscripts. Moreover, journals and regulatory authorities should enforce adherence to these practices prior to publication to enhance transparency, reproducibility, and scientific integrity in clinical research.

Future Perspectives

Real-world data should be embraced as complement to traditional trials and, in some cases, as an alternative

Real-world data have a growing clinically significant role in health care evidence. While randomised controlled trials (RCTs) remain the cornerstone of health-evidence and regulatory approval, this thesis emphasises the growing importance of complementing RCT data with real-world evidence to optimise patient care in clinical practice. Real-world data should therefore be embraced as an essential complement to, and sometimes as an alternative for, traditional RCTs.

There is often a substantial discrepancy between the efficacy reported in RCTs and the effectiveness observed in unselected patient populations. This is also known as the efficacy-effectiveness gap[27]. This discrepancy reflects the selective inclusion criteria of clinical trials and the complex and heterogeneous nature of real-world patients. Furthermore, certain subgroups, such as older patients, patients with comorbidities or patients with poor performance status, are often underrepresented or excluded from RCTs[27-30]. Studies based on real-world data are therefore essential for identifying which patients would benefit most from each approach, thus enabling more personalised treatment strategies.

For example, the survival outcomes of patients treated with first-line ipilimumab-nivolumab in the Netherlands are evaluated; these data are not presented in this manuscript, but are currently in preparation. Compared to the intermediate and poor risk ipilimumab-nivolumab arm of the CheckMate-214 trial, a shorter overall survival of 25 months is observed in the real-world cohort, compared to 48 months in the Checkmate trial[31]. Additional subgroup analysis shows a clear difference in median overall survival between CheckMate-eligible and non-eligible patients within the cohort (26 vs. 19 months), highlighting a substantial discrepancy between efficacy demonstrated in a trial and effectiveness in a real-world setting. While the discrepancy can be partially explained by the fact that our cohort exclusively included synchronous metastatic RCC patients, who are known to have a poorer prognosis[32], it also highlights the inherent underrepresentation of certain subgroups in clinical trials[33].

Real-world evidence is also crucial for informing health policy, as pharmaceutical approval and reimbursement policies often encourage the widespread use of therapies in routine practice. Currently, decisions on policies and guidelines are still primarily driven by results from RCTs, but it is increasingly important to incorporate real-world evidence into these processes. Due to rapid developments, many clinically relevant comparisons –such as head-to-head evaluations of new systemic therapies or the optimal timing of cytoreductive interventions– cannot always be fully addressed in traditional RCTs. These trials are often lengthy, costly, and risk becoming outdated by the time results are available[34]. In such cases, real-world data can be used as alternative for RCTs. Such reliance on real-world evidence also implies that guideline development must occasionally proceed in the absence of full level 1 evidence, requiring careful interpretation and transparent reporting of the data used.

PROspective Renal Cell Carcinoma (PRO-RCC)
During this PhD trajectory, the PRO-RCC infrastructure is established to facilitate research with real-world data[35] (**Chapter 8**). This nationwide, prospective, observational registry systematically collects real-world data on patients with both localised and metastatic RCC in the Netherlands. It also collects Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) to assess the impact on quality of life and quality of care. Additionally, the PRO-RCC registry is designed to enable 'Trials Within Cohorts' (TWiCs), offering a practical approach to interventional studies in routine care settings[36]. Altogether, the PRO-RCC cohort will enable clinically relevant research that rapidly translates real-world insights into patient care. This approach aligns with the open access movement, which encourages broad availability of scientific data and results, to accelerate dissemination and implementation of clinically relevant insights.

Beyond head-to-head comparisons of novel therapies and identifying the role of cytoreductive nephrectomy in the immunotherapy era, the PRO-RCC cohort offers many other research opportunities. These include evaluating the effectiveness of adjuvant therapies, clarifying the role of SBRT, integrating biomarker analyses to personalise treatment strategies, and systematically collecting patient-reported outcomes to support shared decision-making.

Conclusion

Overall, real-world data are becoming increasingly important in clinical research. They complement traditional trials by providing insights into populations that are often underrepresented and by supporting the development of more personalised treatment strategies. Furthermore, given the rapid developments in therapeutic landscapes and the practical challenges of conducting large randomised studies, real-world data provide a valuable and feasible alternative to address clinically relevant questions. Registries such as PRO-RCC have many opportunities for future research by systematically collecting real-world data and rapidly translating insights into clinical practice.

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Appendices

Summary

Renal Cancer Management Beyond Clinical Trials – Real-world evidence on Treatment and Outcomes

Kidney cancer -or renal cell carcinoma (RCC)- accounts for approximately 2-3% of all cancers diagnosed worldwide, ranking as the 14th most common malignancy. The incidence of RCC is steadily increasing over recent decades, particularly in Western countries where the highest rates are observed. The incidence of RCC is expected to increase in the coming years due to the growing prevalence of obesity, smoking and hypertension, as well as population growth and ageing. There are specific developments in the treatment of both localised and metastatic RCC in the last decade. Nephron-sparing and minimally invasive treatment options have become available for localised RCC. More recently, the treatment landscape of metastatic RCC has evolved with the introduction of immunotherapies.

This thesis examined various aspects of RCC care using real-world data to analyse trends in treatment and outcomes. Such analysis offer valuable insights into current clinical practices, which can be used to guide and enhance future clinical practice. These studies are presented in the following chapters.

Chapter 2 examines trends in RCC incidence, treatment patterns, and relative survival rates in older versus younger patients over time, in order to identify age-related disparities. A total of 31,591 patients are included. 54% is classified as younger (<70 years), 31% as septuagenarians (70-79 years) and 15% as octogenarians (>80 years). Over the years, octogenarians are less often treated with active therapy, regardless of tumour stage. Benefits of recent advances in systemic treatment are not seen in octogenarians: Three-year relative survival of younger patients with advanced RCC improves between 2011 and 2022 (from 26% to 41%) and in septuagenarians (from 19% to 25%), but this is not observed in octogenarians, with three-year relative survival rates of 12% in 2011-2014, 16% in 2015-2018, and 15% in 2019-2022. As life expectancy continues to increases, it becomes ever more important that treatment decisions are guided by comprehensive evaluations of comorbidity, frailty, and patient preferences, rather than calendar age alone. Such an approach can help ensure that older patients who are likely to benefit from active treatment are not denied access to potentially life-prolonging therapies.

Chapter 3 evaluates variation in the management of cT1 RCC in the Netherlands between 2014 and 2020, with a focus on adherence to the Dutch surgical volume standards for hospitals performing RCC surgery. High-volume centres appear to be more consistent in adhering to the guidelines, particularly with regard to the preferred use of partial nephrectomy over radical nephrectomy in cT1 RCC. Another key finding is the unequal access to focal therapy among patients with cT1a RCC. Geographic differences in the proportion of patients treated with focal therapy are found based on patients' postal codes. It is crucial that all patients have equal access to high-quality healthcare, and a shared decision-making approach should be adopted, in which all treatment options are transparently discussed and carefully considered.

Chapter 4 examines whether upfront cytoreductive nephrectomy (CN) improves the overall survival of patients with metastatic RCC in the immunotherapy era. This nationwide cohort study included all patients diagnosed with synchronous metastatic RCC in the Netherlands between 2018 and 2020, treated with either immunotherapy (IO) or a tyrosine kinase inhibitor (TKI). Overall survival is separately assessed for patients with and without upfront CN, stratified by first-line therapy (IO or TKI). Patients receiving upfront CN differ significantly from patients with first-line IO or TKI in most baseline characteristics. To account for these imbalances, propensity score-based inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier and Cox regression analyses are used to adjust for prognostic differences between patients with and without upfront CN. Among patients treated with IO, IPTW-adjusted median overall survival is 33 months for those with upfront CN versus 24 months for patients without (HR 0.62, 95% CI 0.40–0.97). In contrast, no significant difference is observed among TKI-treated patients (19 months with uCN versus 17 months without; HR 0.76, 95% CI 0.52–1.12). In the absence of randomised controlled trials (RCTs), these results suggest a potential benefit of upfront CN in patients with metastatic RCC with favourable prognostic factors in the IO era. Nevertheless, given the risk of residual confounding, robust evidence from RCTs remains necessary.

Chapter 5 describes the impact of the COVID-19 pandemic on RCC care in the Netherlands, focusing on changes in the number of diagnoses and in treatment during this period. During the first COVID-19 wave in 2020, the number of new RCC diagnoses decreases by 15%. Numbers recover partially later that year; however, the total number of new RCC diagnoses remains approximately 10% lower compared to 2018–2019. The decline is primarily due to a decrease in T1a/T1b RCCs and is most pronounced among patients aged 70 years or older.

Changes in treatment during the first COVID-19 wave are limited and temporary; in accordance with the adapted guidelines, fewer surgeries are performed for T1a RCCs in favour of active surveillance, while in metastatic RCC, targeted therapy is preferred over immunotherapy. The time to initiation of first-line treatment is not prolonged, and no increase in metastatic RCC incidence is observed until the end of 2021. Overall, the impact of the first COVID-19 outbreak on RCC care in the Netherlands is relatively limited and in line with the adapted guidelines.

In **Chapter 6**, the uptake of IO as first-line and later-line treatment in routine clinical practice in the Netherlands is evaluated. In total, 2621 patients are diagnosed with synchronous metastatic RCC between 2018 and 2022. Overall, 55% receives at least one line of systemic therapy, 7% a cytoreductive nephrectomy without systemic therapy, and the remaining 37% best supportive care. Among systemically treated patients, the use of first-line TKI decreases from 94% in 2018 to 21% in 2022, while the use of IO increases from 6% to 79%. Of those receiving first-line systemic therapy, 32% and 10% receives any second-line and third-line treatment, respectively. Three-year overall survival for patients with synchronous metastatic RCC improves significantly over time, from 20% in 2018 to 28% in 2021. This analysis indicates that immunotherapies are rapidly adopted in clinical practice since their approval in 2019, which aligns with current European Association of Urology guideline recommendations.

Primary endpoints are defined in the study protocol of RCTs, and transparency regarding any subsequent changes is essential, given that approvals of novel therapies often rely on these studies. **Chapter 7** evaluates changes in primary endpoints in RCTs, as well as how such changes are reported. This systematic review includes 38 RCTs investigating immunotherapy for bladder, lung and kidney cancer. Of these, 24 studies (63%) modifies at least one aspect of a primary endpoint. The most common modifications involve adding overall survival as an outcome measure and conducting additional comparisons in biomarker-positive patients. Changes occur both early in the study and after the completion of patient inclusion and randomisation. However, only eight of the 24 publications explicitly report modifications to the primary endpoint, and just five provide reasons for the changes, most often citing results from other trials. The lack of clarity regarding modifications to study design and outcomes remains a concern, highlighting the need for greater transparency in RCT reporting.

Chapter 8 describes the aims and infrastructure of the PROspective Renal Cell Carcinoma (PRO-RCC) cohort. PRO-RCC is a multicentre cohort that aims to include all Dutch patients with RCC, with more than 25 hospitals currently participating. In addition to the data routinely collected by the Netherlands Cancer Registry, specific clinical data items concerning patient and tumour characteristics, disease stage and treatment are registered for patients enrolled in the PRO-RCC cohort. These data are collected at diagnosis and during follow-up. Patients also complete online health-related quality of life questionnaires. Furthermore, the PRO-RCC infrastructure enables interventional research to be conducted using the 'Trial Within Cohorts' (TwiCs) design. The TwiCs design eliminates some issues that are experienced in RCTs, such as slow patient accrual and the risk of dropping out due to disappointment after randomisation. In summary, PRO-RCC is an initiative to construct a nationwide long-term cohort of RCC patients in the Netherlands, enabling collection of long-term clinical data, patient reported outcome measures (PROMs) and patient reported experience measures (PREMs) to facilitate observational research. Furthermore, interventional studies can be conducted with the TwiCs design.

Chapter 9 provides a general discussion of all studies described in this thesis and specific recommendations based on the findings of these studies are formulated. In addition, future perspectives and opportunities are discussed.

Overall, this thesis underscores the growing importance of real-world evidence for clinical practice. The studies presented here highlight both the advancements that have been achieved and the remaining gaps that require further investigation. Looking ahead, the PRO-RCC infrastructure will continue to facilitate such research with the aim to improve the quality of care of RCC further.

Nederlandse samenvatting

Nierkankerzorg in de dagelijkse praktijk – inzichten in behandeling en uitkomsten

Nierkanker maakt ongeveer 2-3% uit van alle kankergevallen wereldwijd en is daarmee de 14e meest voorkomende vorm van kanker. De incidentie van nierkanker is de afgelopen decennia toegenomen, vooral in Westerse landen waar de hoogste aantallen worden waargenomen. Verwacht wordt dat de incidentie van nierkanker in de komende jaren zal blijven stijgen door de toenemende prevalentie van obesitas, roken en hypertensie, evenals door bevolkingsgroei en vergrijzing. In de afgelopen decennia zijn er specifieke ontwikkelingen geweest in de behandeling van zowel gelokaliseerde als uitgezaaide nierkanker. Niersparende en minimaal invasieve behandelopties zijn beschikbaar geworden voor gelokaliseerde nierkanker. Meer recentelijk is de behandeling van uitgezaaide nierkanker veranderd door de introductie van immuuntherapie.

In dit proefschrift worden verschillende aspecten van nierkankerzorg onderzocht met behulp van data uit de dagelijkse praktijk (*real-world data*) om trends in behandeling en uitkomsten te analyseren. Dergelijke analyses bieden waardevolle inzichten in de huidige klinische praktijk, die gebruikt kunnen worden om toekomstige zorg te verbeteren. De onderzoeken worden gepresenteerd in de volgende hoofdstukken.

In **Hoofdstuk 2** worden trends in nierkanker incidentie, behandeling en overleving bij oudere versus jongere patiënten tussen 2011 en 2022 onderzocht met als doel leeftijdsgerelateerde verschillen te identificeren. Van de in totaal 31.591 patiënten die zijn geïncludeerd in deze studie is 54% geclassificeerd als 'jong' (<70 jaar), 31% als 'zeventigers' (70-79 jaar) en 15% als 'tachtigplussers' (>80 jaar). Tijdens deze periode worden tachtigplussers minder vaak behandeld met actieve therapie, ongeacht het ziektestadium. De driejarige relatieve overleving van jonge patiënten met uitgezaaide ziekte stijgt tussen 2011 en 2022 significant van 26% naar 41%, en bij zeventigers van 19% naar 25%, maar blijft bij tachtigplussers nagenoeg onveranderd (12% in 2011-2014, 16% in 2015-2018 en 15% in 2019-2022), ondanks nieuwe systemische middelen. Naarmate de levensverwachting blijft toenemen, wordt het steeds belangrijker dat behandelbeslissingen worden gebaseerd op een uitgebreide evaluatie van comorbiditeiten, kwetsbaarheid en voorkeuren van de patiënt, in plaats van alleen op kalenderleeftijd. Een dergelijke benadering verbetert de selectie van oudere patiënten die eveneens baat kunnen hebben bij een actieve behandeling.

Hoofdstuk 3 richt zich op de behandeling van T1 nierkanker in Nederland tussen 2014 en 2020. Dit zijn kleine tumoren die beperkt zijn tot de nier en volgens de richtlijn bij voorkeur niersparend worden behandeld. In deze periode houden ziekenhuizen met een hoog operatievolume zich vaker aan de richtlijnen, vooral wat betreft het gebruik van partiële nefrectomie in plaats van radicale nefrectomie bij T1-tumoren. Daarnaast hebben patiënten met niertumoren tot 4 cm (T1a) geen gelijke toegang tot focale therapie. Er zijn namelijk verschillen in het percentage patiënten met deze behandeling afhankelijk van hun postcode. Het is essentieel dat alle patiënten toegang hebben tot gelijke zorg. Daarom moet in de spreekkamer gedeelde besluitvorming (*shared decision making*) worden toegepast, waarbij alle behandelopties besproken worden en zorgvuldig worden afgewogen.

Hoofdstuk 4 onderzoekt of het operatief verwijderen van nierkanker vóór systemische behandeling (cytoreductieve nefrectomie) de overleving van patiënten met uitgezaaide nierkanker in combinatie met immuuntherapie verbetert. In deze landelijke studie zijn alle patiënten geïncludeerd met uitgezaaide nierkanker bij diagnose, die behandeld zijn met immuuntherapie of doelgerichte therapie middels tyrosinekinaseremmers tussen 2018 en 2020 in Nederland. De overleving is apart bekeken voor patiënten die wel of geen operatie hebben gekregen en is verder uitgesplitst naar type systemische behandeling (immuuntherapie of doelgerichte therapie). Geopereerde patiënten verschillen significant in een aantal basiskenmerken ten opzichte van patiënten met alleen systemische therapie. Voor deze verschillen is een correctie toegepast. Bij patiënten behandeld met immuuntherapie is de gecorrigeerde mediane overleving significant langer met een operatie, namelijk 33 maanden in vergelijking met 24 maanden bij patiënten zonder operatie (HR 0,62; 95% CI 0,40–0,97). Bij TKI-behandelde patiënten wordt geen significant verschil gevonden: 19 maanden met operatie versus 17 maanden zonder operatie (HR 0,76; 95% CI 0,52–1,12). Deze resultaten suggereren een mogelijk voordeel van een cytoreductieve nefrectomie bij patiënten met uitgezaaide nierkanker die gunstige prognostische factoren hebben. Toch blijft robuust bewijs uit gerandomiseerde onderzoeken noodzakelijk, vanwege het risico op verschillen tussen groepen die niet gecorrigeerd konden worden.

Hoofdstuk 5 beschrijft de impact van de COVID-19 pandemie op de nierkankerzorg in Nederland, waarbij is gekeken naar veranderingen in het aantal diagnoses en de gegeven behandelingen tijdens deze periode. Tijdens de eerste COVID-19 piek in 2020 daalt het aantal nieuwe nierkankerdiagnoses

met 15%. Het aantal diagnoses herstelt zich gedeeltelijk later dat jaar, maar blijft ongeveer 10% lager dan in 2018 en 2019. De daling wordt voornamelijk veroorzaakt door een afname van T1 nierkanker en was het meest uitgesproken bij patiënten van 70 jaar of ouder. Veranderingen in behandeling tijdens de eerste piek zijn beperkt en tijdelijk. Conform de aangepaste richtlijnen zijn er minder operaties uitgevoerd bij T1a nierkanker ten gunste van actief vervolgen (*actieve surveillance*), terwijl bij uitgezaaide nierkanker doelgerichte therapie is verkozen boven immuuntherapie. De tijd tot aanvang van eerstelijnsbehandeling is niet verlengd, en er is geen toename in uitgezaaide nierkanker tot eind 2021. Concluderend is de impact van de eerste COVID-19 uitbraak op de nierkankerzorg in Nederland relatief beperkt en in lijn met de aangepaste richtlijnen.

Hoofdstuk 6 evalueert het gebruik van immuuntherapie in de dagelijkse klinische praktijk in Nederland. Tussen 2018 en 2022 zijn in totaal 2621 patiënten gediagnosticeerd met uitgezaaide nierkanker bij diagnose. Van deze patiënten is 55% behandeld met systemische therapie, 7% met een cytoreductieve nefrectomie zonder systemische behandeling, en de overige 37% met palliatieve zorg gericht op comfort (*best supportive care)*. Bij de systemisch behandelde patiënten is het gebruik van doelgerichte therapie met tyrosinekinaseremmers afgenomen van 94% in 2018 tot 21% in 2022. Tegelijkertijd stijgt het gebruik van immuuntherapie van 6% naar 79%. Van de patiënten met systemische behandeling krijgt 32% een tweede- en 10% een derde behandeling met een ander systemische middel. De driejarige overleving van patiënten met uitgezaaide nierkanker bij diagnose is significant verbeterd van 20% in 2018 tot 28% in 2021. Ook bij patiënten met systemische behandeling stijgt de overleving van 26% naar 33%. Deze analyse laat zien dat immuuntherapieën sinds hun goedkeuring in 2019 snel zijn geïmplementeerd in de klinische praktijk, in lijn met de huidige Europese richtlijnen.

Primaire eindpunten worden vastgelegd in het studieprotocol van gerandomiseerde studies. Het is essentieel dat eventuele wijzigingen hierin transparant worden gerapporteerd, omdat goedkeuringen van nieuwe therapieën vaak afhankelijk zijn van deze studies. **Hoofdstuk 7** onderzoekt veranderingen in de primaire eindpunten van gerandomiseerde studies en of deze wijzigingen worden gerapporteerd in publicaties. Deze review omvatte 38 studies die immuuntherapie onderzoeken bij blaaskanker, longkanker en nierkanker. 24 studies (63%) passen ten minste één aspect van een primair eindpunt aan. De meest voorkomende aanpassingen zijn het toevoegen van

algehele overleving als uitkomstmaat en het uitvoeren van extra analyses bij biomarker-positieve patiënten. Wijzigingen vonden zowel vroeg in de studie plaats als na voltooiing van patiëntinclusie en randomisatie. Slechts 8 van de 24 publicaties melden expliciet dat het primaire eindpunt is aangepast, en slechts 5 geven ook een reden voor de wijziging, meestal gebaseerd op resultaten van andere studies. Het is zorgwekkend dat aanpassingen in het ontwerp van gerandomiseerde studies vaak niet goed worden toegelicht en het benadrukt het belang van meer transparantie en rapportage bij wijzigingen van primaire eindpunten.

Hoofdstuk 8 beschrijft de doelstellingen en infrastructuur van PRO-RCC (*PROspective Renal Cell Carcinoma)*. PRO-RCC is een landelijke studie met het doel om data te verzamelen van alle Nederlandse patiënten met nierkanker. Met deze gegevens kan vervolgens onderzoek worden gedaan. Momenteel doen meer dan 25 ziekenhuizen mee. Gegevens over patiënt- en tumorkenmerken, ziektestadium en behandelingen worden in de Nederlandse Kanker Registratie geregistreerd. Deze informatie wordt zowel bij diagnose als tijdens de follow-up vastgelegd. Patiënten vullen daarnaast online vragenlijsten in over hun kwaliteit van leven. De PRO-RCC infrastructuur maakt ook interventiestudies mogelijk met behulp van het '*Trial Within Cohorts*' (TwiCs) ontwerp. Dit ontwerp lost enkele problemen op die bij traditionele RCTs kunnen optreden, zoals trage patiëntinclusie of het risico dat patiënten stoppen met de studie uit teleurstelling na randomisatie. Samengevat biedt PRO-RCC de mogelijkheid om klinische gegevens en vragenlijsten van patiënten met nierkanker te verzamelen voor observationeel onderzoek, en tegelijkertijd interventiestudies uit te voeren via het TwiCs-ontwerp.

Hoofdstuk 9 bevat een algemene discussie van de studies in dit proefschrift en specifieke aanbevelingen op basis van de bevindingen van deze studies. Daarnaast worden toekomstige perspectieven en mogelijkheden besproken. Samengevat benadrukt dit proefschrift het groeiende belang van *real-world evidence* voor de klinische praktijk. Zowel de geboekte vooruitgang als de resterende kennislacunes waarvoor verder onderzoek nodig is, worden zichtbaar aan de hand van de gepresenteerde studies. Vooruitkijkend zal de PRO-RCC infrastructuur dit soort onderzoek blijven ondersteunen, met als doel de kwaliteit van zorg voor alle nierkankerpatiënten verder te verbeteren.

Authors contributions

Study Conception and design	1
Acquisition of data	2
Analysis and interpretation of data	3
Drafting of manuscript	4
Critical Revisions	5

Chapter 1 – General Introduction and Outline of Thesis

H. Yildirim	1,4
P.J. Zondervan, A.D. Bins, K.K.H. Aben	5

Chapter 2 - Trends in Treatment and Survival of Older versus Younger Patients with Renal Cancer between 2011-2022

H. Yildirim, M.S. Schuurman	1,3,4
H.H.E. van Melick, A.D. Bins, P.J. Zondervan	5
K.K.H. Aben	1,3,4,5

Chapter 3 – Variation in the Management of cT1 Renal Cancer by Surgical Hospital Volume: A Nationwide Study.

H. Yildirim	1,3,4
M.S. Schuurman	3,4
C.V. Widdershoven, B.W. Lagerveld, L. van den Brink, A.E.C. Ruiter, H.P. Beerlage, R.J.A. van Moorselaar, N.M. Graafland, A. Bex,	5
K.K.H. Aben, P.J. Zondervan	1,5

Chapter 4 – A Nationwide Real-World Evaluation of Upfront Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma in the Immunotherapy Era.

H. Yildirim	1,3,4
M.J. Bijlsma	3,4
A.W. Postema, M.J.B. Aarts, M.G.H. van Oijen	5
K.K.H Aben, A. Bex, A.D. Bins, P.J. Zondervan	1,5

Chapter 5 – The Impact of the COVID-19 Pandemic on Renal Cancer Care.

H. Yildirim	1,3,4
A.D. Bins, C. van den Hurk, R.J.A. van Moorselaar, M.G.H. van Oijen, A. Bex	5
P.J. Zondervan, K.K.H. Aben	1,5

Chapter 6 – Immunotherapy in Metastatic Renal Cell Carcinoma: Insights from a Dutch Nationwide Cohort.

H. Yildirim	1,3,4
A. Richters, K.K.H. Aben	4,5
A.D. Bins, A.W. Postema, M.J.B. Aarts, M.G.H. van Oijen, P.J. Zondervan	5

Chapter 7 – Changes to Primary End Points in Randomized Clinical Trials on Immune Checkpoint Inhibitors in Urothelial, Renal Cell, and Lung Cancers: A Systematic Review.

A. Richters	1,2,3,4
H. Yildirim	2,3,4
C.M. Booth, F.E. Vera Badillo, L.A.L.M. Kiemeney, K.K.H. Aben	5

Chapter 8 – The PRO-RCC Study: A Long-Term PROspective Renal Cell Carcinoma Cohort in the Netherlands, Providing an Infrastructure for 'Trial within Cohorts' Study Designs.

H. Yildirim	1,3,4
C.V. Widdershoven, M.J.B. Aarts, A. Bex, H.J. Bloemendal ,D. M. Bochove-Overgaauw,	5
P. Hamberg, K.H. Herbschleb, T. van der Hulle, B.W. Lagerveld, M.G.H. van Oijen, S.F. Oosting, J.V. van Thienen, A.A.M. van der Veldt, H.M. Westgeest, E.E. Zeijdner, K.K.H. Aben, C. van den Hurk, P.J. Zondervan, A.D. Bins	1,5

Chapter 9 – General Discussion and Future Perspectives.

H. Yildirim	1,4
P.J. Zondervan, A.D. Bins, K.K.H. Aben	5

PhD Portfolio

PhD candidate: Hilin Yildirim
PhD period: May 2021 – June 2025
Affiliation: Amsterdam University Medical Centers, University of Amsterdam, location VUmc, Department of Oncology, Department of Urology.
Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Department of Research and Development.
PhD (co-)supervisors: Dr. A.D. Bins, Dr. P.J. Zondervan, Dr. K.K.H. Aben

	Year	Workload (ECTS)
General courses		
eBROK	2021	2.0
Project management	2021	0.6
Basics in oncology	2022	2.0
Ethics and Integrity in Science	2022	2.0
Practical Biostatistics	2023	1.4
Herregistratie eBROK	2025	0.5
Specific courses		
Trusted Advisory (training)	2023	1.0
Seminars, workshops and master classes		
Two-weekly research meeting urology researchers AmsterdamUMC & AVL	2021-2025	2.0
Three-weekly research meeting IKNL researchers	2021-2025	2.0
Attendance and oral presentation at the Dutch Renal Cancer Group (DRCG) meetings	2022-2024	1.5
Supervising		
Lisan de Beijer (Master thesis biomedical Sciences, Radboud University), real-world outcomes of ipilimumab/nivolumab, IKNL	2024	2.0
Noor Verboom (Master thesis, Oncology VUmc), Health related quality of life of renal cell carcinoma patients, Department of Urology, VUmc	2024	2.0
Other		
Medical Business Projects	2021	2.0

	Year	Workload (ECTS)
Lecturing		
Theoretical and practical teaching in urology (master students medicine UVA)	2023-2024	1.0
Clinical training in Urology (master students medicine VUmc)	2024	0.5
Presentations		
EAU Amsterdam (abstract presentation): *Variation in the management of cT1 renal cancer by surgical hospital volume: A nationwide study*	2022	0.5
EMUC Budapest (poster): *Impact of the COVID-19 pandemic on kidney cancer care in the Netherlands*	2022	0.5
EMUC Marseille (poster): *A nationwide real-world comparison of old vs. new clinical practice for cytoreductive nephrectomy in metastatic renal cell carcinoma*	2023 2024	0.5 0.5
EMUC Lisbon (abstract presentation): *A nationwide real-world evaluation of cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma in the IO era*	2025	0.5
EAU Madrid (poster presentation): *Nationwide trends in treatment and survival of older patients with renal cell caricnoma*	2025	0.5
EAU Madrid (abstract presentation): *Nationwide real-world outcomes of patients with synchronous metastatic renal cell carcinoma treated with ipilimumab/nivolumab*	2022-2024	1.0
DRCG meeting (presentation): *Prospective renal cell carcinoma cohort (PRO-RCC)*		
(Inter)national conferences		
EAU Amsterdam	2022	2.0
NVU voorjaarsvergadering	2022	1.0
EMUC Budapest	2022	2.0
NVU voorjaarsvergadering	2023	1.0
EMUC Marseille	2023	2.0
EMUC Lisbon	2024	2.0
EAU Madrid	2025	2.0

	Year	Workload (ECTS)
Other Conferences and retreats		
OOA PhD retreat (with abstract presentation)	2023	2.0
CCA retreat (with oral/poster presentation)	2022-2024	3.0
Awards and Prizes		
EAU highlight renal cancer	2022	
Highly rated abstract, EMUC, Marseille	2023	
Best oral presentation, EMUC, Lisbon	2024	
Total ECTS		**43.5**

List of Publications

Publications included in this thesis

A Nationwide Real-world Evaluation of Upfront Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma in the Immunotherapy Era.
Yildirim H, Aben KKH, Bijlsma MJ, Postema AW, Aarts MJB, van Oijen MGH, Bex A, Bins AD*, Zondervan PJ*.
European Urology Oncology. 2025;8:623-631. doi: 10.1016/j.euo.2025.02.011.

Immunotherapy in metastatic renal cell carcinoma: Insights from a Dutch nationwide cohort.
Yildirim H, Richters A, Bins AD, Postema AW, Aarts MJB, van Oijen MGH, Zondervan PJ, Aben KKH.
European Urology Open Science. 2025;72:42-45. doi: 10.1016/j.euros.2025.01.008.

Trends in treatment and survival of older vs younger patients with renal cancer between 2011-2022.
Yildirim H*, Schuurman MS*, van Melick HHE, Bins AD, Zondervan PJ, Aben KKH.
British Journal of Urology International. Accepted, November 2025.

The impact of the COVID-19 pandemic on renal cancer care.
Yildirim H, Bins AD, Van den Hurk C, Van Moorselaar RJA, Van Oijen MGH, Bex A, Aben KKA*, Zondervan PJ*.
World Journal of Urology. 2024;42:231. doi: 10.1007/s00345-024-04925-2.

Variation in the management of cT1 renal cancer by surgical hospital volume: A nationwide study.
Yildirim H, Schuurman MS, Widdershoven CV, Lagerveld BW, van den Brink L, Ruiter AEC, Beerlage HP, van Moorselaar RJA, Graafland NM, Bex A, Aben KKH, Zondervan PJ.
BJUI Compass. 2023;4:455-463. doi: 10.1002/bco2.229.

The PRO-RCC study: a long-term PROspective Renal Cell Carcinoma cohort in the Netherlands, providing an infrastructure for 'Trial within Cohorts' study designs.
Yildirim H, van Widdershoven C, Aarts MJB, Bex A, Bloemendal HJ, Bochove-Overgaauw DM, Hamberg P, Herbschleb KH, van der Hulle T, Lagerveld BW,

van Oijen MGH, Oosting SF, van Thienen JV, van der Veldt AAM, Westgeest HM, Zeijdner EE, Aben KKH*, van den Hurk C*, Bins AD*, Zondervan PJ*.
BMC Cancer. 2023;23:648. doi: 10.1186/s12885-023-11094-9.

Changes to primary end points in randomized clinical trials on immune checkpoint inhibitors in urothelial, renal cell, and lung cancers: A systematic review.
Richters A, **Yildirim H**, Booth CM, Badillo FEV, Kiemeney LALM, Aben KKH.
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About the author

Hilin Yildirim was born on the 17th of January 1993 in the Hague, the Netherlands. After finishing her pre-university education at Gymnasium Haganum, she started with Medicine at the University of Utrecht in 2011. During her studies, Hilin worked on research projects, resulting in two publications and a scientific internship in New York. Towards the end of her studies, Hilin developed a particular interest in urology. After receiving her Master's degree, Hilin started working as a urology resident not-in-training. Her interests in clinical practice and scientific research were brought together in a PhD trajectory focused on kidney cancer. This enabled her to develop her scientific and organisational skills further. While working as a clinical researcher at the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL) and the Amsterdam University Medical Centres (Amsterdam UMC), Hilin was the coordinating investigator of the PROspective Renal Cancer Cohort (PRO-RCC) study. She also conducted research on kidney cancer care, using nationwide real-world data to evaluate treatment patterns and outcomes, which resulted in this thesis.

Hilin has currently started her urology residency at the Surgical Department of the 'Onze Lieve Vrouwen Gasthuis' (OLVG) in Amsterdam. She will continue her residency at the Department of Urology of the 'Noordwest Ziekenhuisgroep' and the 'Amsterdam University Medical Centers'.